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(71) Applicant: THE BURNHAM INSTITUTE [US/US], 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors: REED, John, C.; 17044 El Camino Real, Rancho Santa Fe, CA 92067 (US). TAKAYAMA, Shinichi, 390 Stratford Court #3, Del Mar, CA 92014 (US).

(74) Agents: WONG, James, J. et al.; Campbell & Flores LLP, Suite 700, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).

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(57) Abstract

The present invention provides a family of BAG–1 related proteins from humans (BAG–1L, BAG–1, BAG–2, BAG–3, BAG–4 and BAG–5), the invertebrate *C. elegans* (BAG–1, BAG–2) and the fission yeast *S. pombe* (BAG–1A, BAG–1B) and the nucleic acid molecules that encode them.

NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

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This invention was made with government support under grant number CA-67329 awarded by the National Institutes of Health. The United States Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention relates generally to the fields of molecular biology and molecular medicine and more specifically to a novel family of proteins that can regulate protein folding. The functions of these proteins are potentially diverse, including promoting tumor cell growth and metastasis.

BACKGROUND INFORMATION

The Hsc70/Hsp70-family of molecular chaperones participate in protein folding reactions, controlling protein bioactivity, degradation, complex assembly/disassembly, and translocation across membranes. These proteins interact with hydrophobic regions within target proteins via a carboxyl (C)-terminal peptide binding domain, with substrate binding and release being controlled by the N-terminal ATP-binding domain of Hsc70/Hsp70. Hsc70/Hsp70-assisted folding reactions are accomplished by repeated cycles of peptide binding, refolding, and release,

which are coupled to ATP hydrolysis by the ATP-binding domain (ATPase) of Hsc70/Hsp70 and by subsequent nucleotide exchange. The chaperone activity of mammalian Hsc70/Hsp70 is regulated by partner proteins that either modulate the peptide binding cycle or that target the actions of these chaperones to specific proteins and subcellular compartments. DnaJ-family proteins (Hdj-1/Hsp40; Hdj-2; Hdj-3) stimulate the ATPase activity of Hsc70/Hsp70, resulting in the ADP-bound state which binds tightly to peptide substrates. The Hip protein collaborates with Hsc70/Hsp70 and DnaJ homologues in stimulating ATP hydrolysis, and thus also stabilize Hsc70/Hsp70 complexes with substrate polypeptides, whereas the Hop protein may provide co-chaperone functions through interactions with the C-terminal peptide binding domain.

The Bcl-2 associated athanogene-1 (bag-1) is named from the Greek word *athanos*, which refers to anti-cell death. BAG-1 was previously referred to as Bcl-2-associated protein-1 (BAP-1) in U.S. Patent No. 5,539,094 issued July 23, 1996, which is incorporated herein by reference. In this earlier patent, BAG-1 is described as a portion of the human BAG-1 protein, absent the N-terminal amino acids 1 to 85. In addition, a human protein essentially identical to human BAG-1 was described by Zeiner and Gehring, (*Proc. Natl. Acad. Sci., USA* **92**:11465-11469 (1995)). Subsequent to the issuance of U.S. Patent 5,539,094 the N-terminal amino acid sequence from 1 to 85 of human BAG-1 was reported.

BAG-1 and its longer isoforms BAG-1M (Rap46) and BAG-1L are recently described Hsc70/Hsp70-regulating proteins. BAG-1 competes with Hip for binding to the Hsc70/Hsp70 ATPase domain and promotes substrate release. BAG-1 also reportedly stimulates Hsc70-mediated ATP

hydrolysis by accelerating ADP/ATP exchange, analogous to the prokaryotic GrpE nucleotide exchange protein of the bacterial Hsc70 homologue, DnaK. Gene transfection studies indicate that BAG-1 proteins can influence a wide variety of cellular phenotypes through their interactions with Hsc70/Hsp70, including increasing resistance to apoptosis, promoting cell proliferation, enhancing tumor cell migration and metastasis, and altering transcriptional activity of steroid hormone receptors.

Despite the notable progress in the art, there remains an unmet need for the further identification and isolation of additional homologous BAG protein species, and the nucleic acid molecules and/or nucleotide sequences that encode them. Such species would provide additional means by which the identity and composition of the BAG domain, that is, the portion of the protein that is influencing or modulating protein folding, could be identified. In addition, such species would be useful for identifying agents that modulate apoptosis as candidates for therapeutic agents, in particular, anticancer agents. The present invention satisfies these need, as well as providing substantial related advantages.

SUMMARY OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO: 4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)] , the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)] and the nucleic acid molecules that encode them.

Another aspect of the present invention provides an amino acid sequence present in the family of BAG-1 related proteins, that modulates Hsc70/Hsp70 chaperone activity, that is, the BAG domain.

Another aspect of the present invention provides novel polypeptide and nucleic acid compositions and methods useful in modulating Hsc70/Hsp70 chaperone activity.

Another aspect of the present invention is directed to methods for detecting agents that modulate the binding of the BAG family of proteins, such as BAG-1 (beginning at residue 116 of SEQ ID NO:2), and related proteins with the Hsc70/Hsp70 Family of proteins or with other proteins that may interact with the BAG-Family proteins.

Still another aspect of the present invention is directed to methods for detecting agents that induce the dissociation of a bound complex formed by the association of BAG-Family proteins with Hsc70/Hsp70 Family molecule chaperones or other proteins.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the full length cDNA sequence for human BAG-1 (SEQ ID NO:1) protein with the corresponding amino acid sequence (SEQ ID NO:2). Within the full length sequence are included the overlapping sub-sequences of BAG-1 (beginning at nucleotide 391), BAG-1M [beginning at nucleotide 260 of (SEQ ID NO:2)], and BAG-1L [beginning at nucleotide 46 of (SEQ ID NO:2)].

Figures 2A and 2B combined shows the full length cDNA sequence (SEQ ID NO:3) aligned with the corresponding amino acid residues for human BAG-2 protein (SEQ ID NO:4).

Figure 3 shows a cDNA sequence (SEQ ID NO:5) aligned with the corresponding amino acid residues for human BAG-3 protein (SEQ ID NO:6).

Figure 4 shows the a cDNA sequence (SEQ ID NO:7) aligned with the corresponding amino acid residues for human BAG-4 protein (SEQ ID NO:8).

Figure 5 shows a cDNA sequence (SEQ ID NO:9) aligned with the corresponding amino acid residues for human BAG-5 protein (SEQ ID NO:10).

Figure 6A shows the full length cDNA sequence for *C. elegans* BAG-1 protein (SEQ ID NO:11).

Figure 6B shows the 210 amino acid sequence for *C. elegans* BAG-1 protein (SEQ ID NO:12).

Figure 7A shows the full length cDNA sequence for *C. elegans* BAG-2 protein (SEQ ID NO:13).

Figure 7B shows the 458 amino acid sequence for *C. elegans* BAG-2 protein (SEQ ID NO:14).

Figure 8A shows the full length cDNA sequence for *S. pombe* BAG-1A protein (SEQ ID NO:15).

Figure 8B shows the 195 amino acid sequence for *S. pombe* BAG-1A protein (SEQ ID NO:16).

Figure 9A shows the full length cDNA sequence for *S. pombe* BAG-1B protein (SEQ ID NO:17).

Figure 9B shows the 206 amino acid sequence for *S. pombe* BAG-1B protein (SEQ ID NO:18).

Figure 10 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). (A) The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown. (B) The amino acid sequences of the BAG domain for human BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10), *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18), and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14) are aligned demonstrating their homology. Black and gray shading represent identical and similar amino acids, respectively.

Figure 11 shows assays demonstrating the interaction of BAG-family proteins with Hsc70/ATPase. (A) Two-hybrid assays using yeast expressing the indicated fusion proteins. Blue color indicates a positive interaction, resulting in activation of the *lacZ* reporter gene. (B) *In vitro* protein assays using GST-fusion proteins and ^{35}S-labeled *in vitro* translated proteins. (C) Co-immunoprecipitation assays using anti-Flag or IgG1 control antibodies and lysates from 293T cells expressing Flag-tagged BAG-1 (beginning at residue 116 of SEQ ID

NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), Daxx, or Apaf-1.

Figure 12 shows surface plasmon resonance analysis of BAG-family protein interactions with Hsc70/ATPase. (A) SDS-PAGE analysis of purified recombinant proteins. (B) Representative SPR results of biosensor chips containing immobilized BAG proteins with and without maximally bound Hsc70/ATPase.

Figure 13 shows representative SPR results for biosensor chips containing immobilized BAG-1 (beginning at residue 116 at SEQ ID NO:2), BAG-1(ΔC), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) proteins. Hsc70/ATPase was flowed over the chips (arrow/left) until maximal binding was reached (response units), then flow was continued without Hsc70/ATPase (arrow/right). For BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6), Hsc70 was injected at 0.0175, 0.035, 0.07, 0.14, and 0.28 μM.

Figure 14 shows BAG-family protein modulation of Hsc70 chaperone activity. (A) Protein refolding assay of chemically-denatured luciferase by Hsc70 plus DnaJ in the absence or presence of BAG and BAG-mutant proteins. (B) Concentration-dependent inhibition of Hsc70-mediated protein refolding by BAG-family proteins [BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6)] but not by BAG-mutant (BAG-1 (ΔC). (C) Hsc70/Hsp40-mediated refolding of heat-denatured luciferase was assayed in the presence of (black bars) or absence of (striped bars) of 1.8 μM Hip, with (lanes 3-10) or without (lanes 1,2) various BAG-family proteins (1.8μM) as indicated (mean ±SE; n=3). A control (CNTL) is shown (lane 1) in which Hsc70 was replaced with an equivalent amount of BSA.

Figure 15A shows an expanded cDNA sequence for human BAG-3 protein (SEQ ID NO:19).

Figure 15B shows the corresponding amino acid residues for the human BAG-3 protein (SEQ ID NO:20) of Figure 15A.

Figure 15C shows the expanded cDNA sequence (SEQ ID NO:19) aligned with the corresponding amino acid residues for human BAG-3 protein of Figure 15A (SEQ ID NO:20).

Figure 16A shows an expanded cDNA sequence for human BAG-4 protein (SEQ ID NO:21).

Figure 16B shows the corresponding amino acid residues for the human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 16C shows the expanded cDNA sequence (SEQ ID NO:21) aligned with the corresponding amino acid residues for human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 17A shows an expanded cDNA sequence for human BAG-5 protein (SEQ ID NO:23).

Figure 17B shows the corresponding amino acid residues for the human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 17C shows the expanded cDNA sequence (SEQ ID NO:23) aligned with the corresponding amino acid residues for human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 18 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), expanded BAG-3 (SEQ ID NO:20), expanded BAG-4 (SEQ ID NO:22), expanded BAG-5 (SEQ ID NO:24); *S.pombe* BAG-1A (SEQ ID NO:16)and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12)and BAG-2 (SEQ ID NO:14). The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown.

Definitions

The term "apoptosis", as used herein, refers to the process of programmed cell death, although not all programmed cell deaths occur through apoptosis, as used herein, "apoptosis" and "programmed cell death" are used interchangeably.

The term "tumor cell proliferation", as used herein refers to the ability of tumor cells to grow and thus expand a tumor mass.

The term "cell migration", as used herein refers to the role cell motility plays in the invasion and potentially metastasis by tumor cells.

The term "metastasis", as used herein refers to the spread of a disease process from one part of the body to another, as in the appearance of neoplasms in parts of the body remote from the site of the primary tumor; results in dissemination of tumor cells by the lymphatics or blood vessels or by direct extension through serious cavitites or subarachnoid or other spaces.

The term "steroid hormone receptor function", as used herein refers to physiological, cellular and molecular functioning of receptors sites that bind with steroid hormones.

The term "substantially purified", as used herein, refers to nucleic acid or amino acid sequence that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, and most preferably 90% free from other components with which they are naturally associated.

"Nucleic acid molecule" as used herein refers to an oligonucleotide, nucleotide, or polynucleotide, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin which may be single or double stranded, and represent the sense or antisense strand.

"Hybridization", as used herein, refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The terms "complementary" or "complementarity", as used herein, refer to the natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing. For example, the sequence "A-G-T binds to the complementary sequence "T-C-A".

The term "homology", as used herein, refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The inhibition of

hybridization of the completely complementary sequence to the target sequence may be examined using a hybridzation assay (Southern or northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence or probe to the target sequence under conditions of low stringency.

The term "antisense", as used herein, refers to nucleotide sequences which are commplementary to a specific DNA or RNA sequence. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. Antisense molecules may be produced by any method, including synthesis by ligating the gene(s) of interest in a reverse orientation to a viral promoter which permits the synthesis of a complementary strand. Once introduced into a cell, this transcribed strand combines with natural sequences produced by the cell to form duplexes. These duplexes then block either the further transcription or translation. In this manner, mutant phenotypes may be generated. The designation "negative" is sometimes used in reference to the antisense, and "positive" is sometimes used in reference to the sense strand.

"Amino acid sequence" as used herein refers to an oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited herein this term excludes an amino acid sequence of a naturally occurring protein. "Amino acid sequence", "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "functional fragments" or "fragments", as used herein, with regard to a protein refers to portions of that protein that are capable of exhibiting or carrying out the activity exhibited by the protein as a whole. The portions may range in size from three amino acid residues to the entire amino acid sequence minus one amino acid. For example, a protein "comprising at least a functional fragment of the amino acid sequence of SEQ ID NO:1", encompasses the full-length of the protein of SEQ ID NO:1 and portions thereof.

A "derivative" of a BAG protein, as used herein, refers to an amino acid sequence that is alterd by one or more amino acids. The derivative may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., substitution of an apolar amino acid with another apolar amino acid (such as replacement of leucine with isoleucine). The derivative may also have "nonconservative" changes, wherein a substituted amino acid has different but sufficiently similar structural or chemical properties that permits such a substitution without adversely effecting the desired biological activity, e.g., replacement of an amino acid with an uncharged polar R group with an amino acid with an apolar R group (such as replacement of glycine with tryptophan), or alternatively replacement of an amino acid with a charged R group with an amino acid with an uncharged Polar R group (such as replacement of lysine with asparagine).

Amino Acids - Apolar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
alanine	methyl	ala	A
valine	2-propyl	aal	V
leucine	2-methylpropyl	leu	L
isoleucine	2-butyl	ile	I
proline	propyl* - cyclized	pro	P
phenylalanine	benzyl	phe	F
trytophan	3-indolylmethl	tyr	W
methionine	methylthioethyl	met	M

Amino Acids - Uncharged Polar R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
glycine	H	gly	G
serine	hydroxymethyl	ser	S
threonine	1-hydroxyethyl	thr	T
cysteine	thiolmethyl	cys	C
tyrosine	4-hydroxyphenylmethyl	tyr	Y
asparagine	aminocarbonylmethyl	asn	N
glutamine	aminocarbonylethyl	gln	Q

Amino Acids - Charged R Groups

Amino Acid	Radical	Abbreviations	
		3-Letter	1-Letter
aspartic acid	carboxymethyl	asp	D
glutamic acid	carboxyethyl	glu	E
lysine	4-aminobutyl	lys	K
arginine	3-guanylpropyl	arg	R
histidine	4-imidazoylmethyl	his	H

Similar minor modifications may also include amino acids deletions or insertions or both. Guidance in determining which amino acid residues may be modified as indicated above without abolishing the desired biological functionality may be determined using computer programs well known in the art, for example, DNASTAR software. In addition, the derivative may also result from chemical modifications to the encoded polypeptide, including but not limited to the following, replacement of hydrogen by an alkyl, acyl, or amino group; esterification of a carboxyl group with a suitable alkyl or aryl moiety; alkylation of a hydroxyl group to form an ether derivative. Further a derivative may also result from the substitution of a L-configuration amino acid with its corresponding D-configuration counterpart.

The term "mimetic", as used herein, refers to a molecule, the structure of which is developed from knowledge of the structure of a protein/polypeptide or portions thereof (such as BAG-1) and, as such, is able to effect some or all of the actions of BAG-1 protein.

"Peptide nucleic acid", as used herein, refers to a molecule which comprises an oligomer to which an amino acid residue, such as lysine, and an amino group have been added. These small molecules, also designated anti-gene agents, stop transcript elongation by binding to their complementary strand of nucleic acid (Nielsen, P.E. et al., *Anticancer Drug Des.* 8:53-63 (1993)).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1S beginning at residue 116 of SEQ ID NO:2, BAG-2 (SEQ ID

NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO: 8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)], the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)], specifically the full length amino acid sequences comprising human BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), and BAG-2 (SEQ ID NO:4) *C. elegans* BAG-1 (SEQ ID NO:12), and BAG-2 (SEQ ID NO:14), and *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and partial sequences comprising human BAG-3 (SEQ ID NO: 6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) and functional fragments thereof. In particular, the invention provides the amino acid sequences comprising human BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) proteins.

Another aspect of the present invention provides the nucleic molecule and nucleotide sequences that encode the family of BAG-1 related proteins from humans [BAG-1 (SEQ ID NO:1), BAG-2 (SEQ ID NO:3), BAG-3 (SEQ ID NO:5) and (SEQ ID NO:19), BAG-4 (SEQ ID NO:7) and (SEQ ID NO:21) and BAG-5 (SEQ ID NO:9) and (SEQ ID NO:23)], the invertebrate C.*elegans* [BAG-1 (SEQ ID NO:11), BAG-2(SEQ ID NO:13)] and the fission yeast S.*pombe* [BAG-1A (SEQ ID NO:15), BAG-1B (SEQ ID NO:17)].

BAG-1L (SEQ ID NO:2) is a multifunctional protein that blocks apoptosis, promotes tumor cell metastasis, and contributes to factor-independent and p53-resistant cell growth. BAG-1L (SEQ ID NO:2) interacts with several types of proteins, including Bcl-2, some tyrosine kinase growth

factor receptors, steroid hormone receptors, and the p53-induced cell cycle regulator Siah-1A.

BAG-1 is a regulator of Hsc70/Hsp70 family molecular chaperones. A carboxyl-terminal domain in this protein binds tightly to the ATPase domains of Hsc70 and Hsp70 (K_D = 1 nM) (Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). BAG-1 modulates the activity of these molecular chaperones, acting as an apparent functional antagonist of the Hsp70/Hsc70-associated protein Hip (3-5)(Höhfeld, J. and Jentsch, S., *EMBO J.* ***16:*** 6209-6216, (1997); Takayama, S., Bimston, D. N., Matsuzawa, S., Freeman, B. C., Aime-Sempe, C., Xie, Z., Morimoto, R. J., and Reed, J. C., *EMBO J.* ***16:*** 4887-96, (1997); Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* ***16:*** 5483-5490, (1997)). In general, protein refolding is accomplished by Hsp70/Hsc70 through repeated cycles of target peptide binding and release, coupled to ATP hydrolysis (Ellis, R., *Curr Biol.* **7**: R531-R533, (1997)). BAG-1 appears to promote substrate release, whereas Hip stabilizes Hsp70/Hsc70 complex formation with target peptides (Höhfeld, J., Minami, Y., and Hartl, F.-U., *Cell.* **83**: 589-598, (1995)). Since each substrate interaction with Hsc70/Hsp70 is unique in terms of the optimal length of time the protein target should remain complexed with Hsc70/Hsp70 for achieving new conformations, the net effect of BAG-1 can be either enhancement or inhibition of the refolding reaction.

The 70kd heat shock family proteins (Hsp70/Hsc70) are essential to a variety of cellular processes and have been implicated in cancer, yet it is unclear how these proteins are regulated *in vivo*. A variety of co-chaperones have been identified which may target Hsp70/Hsc70 to different subcellular compartments or promote their

interactions with specific protein or protein complexes. BAG-1 appears to represent a novel Hsp70/Hsc70 regulator which differs functionally from all other mammalian co-chaperones identified to date, such as members of the DnaJ-, Hip-, Hop-, and cyclophilin-families of proteins.

Another aspect of the present invention provides the amino acid sequence of a binding domain of about 40 to 55 amino acids that bind the a Hsc70/Hsp70 ATPase domain. The BAG domain is situated near the C-terminus, and the ubiquitin-like domains are situated near the N-terminus.

The BAG family of proteins of the present invention contain a common conserved C-terminal domain (the "BAG" domain) that facilitates binding to the ATPase domain of Hsp70/Hsc70. The carboxyl-terminal domain of BAG-1 binds to the ATPase domain of Hsc70/Hsp70 and regulates its chaperone function by acting as a ADP-ATP exchange factor. Other domains of BAG-1 mediate interactions with proteins such as Bcl-2 and retinoic acid receptors (RARs), allowing BAG-1 to target Hsc70/Hsp70 to other proteins, presumably modulating their function by changing their conformations.

Human BAG-1 was previously shown to inhibit Hsc70/Hsp70 dependent refolding of denatured protein substrates *in vitro* (S. Takayama, et al., *EMBO J* **16**, 4887-96 (1997); M. Zeiner, M. Gebauer, U. Gehring, *EMBO J.* **16**, 5483-5490 (1997); and J. Höhfeld, S. Jentsch, *EMBO J.* **16**, 6209-6216 (1997)). In Example III, Part A the effects of recombinant human BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were compared using *in vitro* protein refolding assays similar to those employed previously for assessing BAG-1. The study showed that addition of equimolar amounts of each of the recombinant proteins to Hsc70 resulted in significant inhibition of luciferase refolding, with BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) showing somewhat

greater inhibitor activity than BAG-1 (Figure 4A). In a separate luciferase folding study BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) once again displayed inhibition of luciferase refolding, however in this study varying amounts of BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were added relative to Hsc70 which resulting in concentration-dependent inhibition of Hsc70 chaperone activity, i.e., luciferase folding (Example III Part A). Additional follow on studies using the same experimental protocols as the previous studies, as taught in Example IIA, have shown that BAG-4 (SEQ ID NO:22) also undergoes association with Hsc70/ATPase.

Yet another aspect of the present invention provides a nucleotide sequence having at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides that can hybridize or is complementary under relatively stringent conditions to a portion of the nucleic acid sequences shown in Figures 1-9 and Figures 15-17, in particular the BAG domain as shown in in Figure 1B, e.g., nucleotides 552-593 of human BAG-3, or nucleotides 167-221 of human BAG-4.

Yet another aspect of the present invention provides a compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

X^1 is an amino acid with a charged or uncharged R group, such as aspartic acid, glutamic acid, asparagine, or glutamine;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group, such as glutamic acid;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group, such as leucine, methionine, or isoleucine;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group, such as aspartic acid or glutamine acid;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group, such as leucine, valine, methionine, alanine or threonine;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group, such as arginine, lysine, glutamine or aspartic acid;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group, such as arginine;

X^8 is an amino acid with a charged R group, such as arginine or lysine;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group, such as valine;

R^{10} is a group of 3 independently selected amino acids;

X^{10} is an amino acid with an uncharged R group, such as glutamine;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group, such as leucine; and

R^{C} is a group of 1 to 100 independently selected amino acids.

A nucleotide sequence of at least about 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides can be useful, for example, as a primer for the polymerase chain reaction (PCR) or other similar reaction mediated by a polymerase such as a DNA or RNA polymerase (see PCR Protocols: A guide to methods and applications, ed. Innis et al. (Academic Press, Inc., 1990), which is incorporated herein by reference; see, for example, pages 40-41). In addition, such a nucleotide sequence of the invention can be useful as a probe in a hybridization reaction such as Southern or northern blot analysis or in a binding assay such as a gel shift assay.

A nucleotide sequence of the invention can be particularly useful as an antisense molecule, which can be DNA or RNA and can be targeted to all or a portion of the 5'-untranslated region or of the 5'-translated region of a bag-1 nucleic acid sequence in a cell. For example, an antisense molecule can be directed to at least a portion of the sequence shown as the BAG domain in Figure 1A, e.g., nucleotides 272-319 of human BAG-1L (SEQ ID NO:1), or nucleotides 79-147 of human BAG-5 (SEQ ID NO:9). Since the 5'-region of a nucleic acid contains elements involved in the control of expression of an encoded protein, an antisense molecule directed to the 5'-region of a nucleic

acid molecule can affect the levels of protein expressed in a cell.

A nucleotide sequence of the invention also can be useful as a probe to identify a genetic defect due a mutation of a gene encoding a BAG protein in a cell. Such a genetic defect can lead to aberrant expression of a BAG protein in the cell or to expression of an aberrant BAG protein, which does not properly associate with a Bcl-2-related protein or Hsc70/Hsp70 protein in the cell. As a result, a genetic defect in a gene encoding, for example, human BAG-1 can result in a pathology characterized by increased or decreased levels in protein folding.

Further a nucleotide compound or composition as taught in the present invention can be synthesized using routine methods or can be purchased from a commercial source. In addition, a population of such nucleotide sequences can be prepared by restriction endonuclease or mild DNAse digestion of a nucleic acid molecule that contains nucleotides as shown in the nucleotide sequences shown in Figures 1-9 and Figures 15-17 that encodes the amino acids sequences also shown in Figures 1-9 and Figures 15-17. Methods for preparing and using such nucleotide sequences, for example, as hybridization probes to screen a library for homologous nucleic acid molecules are well known in the art (see, for example, Sambrook et al., *Molecular Cloning: A laboratory manual* (Cold Spring Harbor Laboratory Press 1989); Ausubel et al., *Current Protocols in Molecular Biology* (Green Publ., NY 1989), each of which is incorporated herein by reference).

A particular nucleotide sequence can be designed based, for example, on a comparison of the nucleic acid molecules encoding any one of the BAG family proteins, as shown in Figures 1-9 and Figures 15-17, with another in the family. Such a comparison allows, for example, the

preparation of a nucleotide sequence that will hybridize to a conserved region present in both nucleic acid molecules, thus providing a means to identify homologous nucleic acid molecules present in other cell types or other organisms. In addition, such a comparison allows the preparation of a nucleotide sequence that will hybridize to a unique region of any of the BAG family nucleotide sequences, such as those corresponding to the BAG domain, thus allowing identification of other proteins sharing this motif. In this regard, it is recognized that, while the human BAG-3 proteins shown as Figures 3 and 20, and human BAG-5 proteins shown as Figures 5 and 24, are only partial sequences, a variant human BAG-3 or BAG-5 produced, for example, by alternative splicing can exist and can be identified using an appropriately designed nucleotide sequence of the invention as a probe. Such useful probes readily can be identified by inspection of the sequences shown in the disclosed Figures by a comparison of the encoding nucleotide sequences.

If desired, a nucleotide sequence of the invention can incorporate a detectable moiety such as a radiolabel, a fluorochrome, a ferromagnetic substance, a luminescent tag or a detectable binding agent such as biotin. These and other detectable moieties and methods of incorporating such moieties into a nucleotide sequence are well known in the art and are commercially available. A population of labelled nucleotide sequences can be prepared, for example, by nick translation of a nucleic acid molecule of the invention (Sambrook et al., *supra*, 1989; Ausubel et al., *supra*, 1989).

One skilled in the art would know that a method involving hybridization of a nucleotide sequence of the invention can require that hybridization be performed under relatively stringent conditions such that nonspecific background hybridization is minimized. Such hybridization

conditions can be determined empirically or can be estimated based, for example, on the relative GC content of a sequence and the number of mismatches, if known, between the probe and the target sequence (see, for example, Sambrook et al., *supra*, 1989).

The invention further provides antibodies specific for human BAG family protein. As used herein, the term "antibody" includes polyclonal and monoclonal antibodies, as well as polypeptide fragments of antibodies that retain a specific binding activity for human BAG-1 of at least about 1 x 10^5 M^{-1}. One skilled in the art would know that anti-BAG-1 antibody fragments such as Fab, $F(ab')_2$ and Fv fragments can retain specific binding activity for human BAG-1 (beginning at residue 116 of SEQ ID NO:2) and, thus, are included within the definition of an antibody. In addition, the term "antibody" as used herein includes naturally occurring antibodies as well as non-naturally occurring antibodies and fragments that retain binding activity such as chimeric antibodies or humanized antibodies. Such non-naturally occurring antibodies can be constructed using solid phase peptide synthesis, can be produced recombinantly or can be obtained, for example, by screening combinatorial libraries consisting of variable heavy chains and variable light chains as described by Huse et al., *Science* **246**:1275-1281 (1989), which is incorporated herein by reference.

One skilled in the art would know that purified BAG family protein, which can be prepared from natural sources or synthesized chemically or produced recombinantly, or portions of a BAG family protein, including a portion of human BAG family protein such as a synthetic peptide as described above, can be used as an immunogen. Such peptides useful for raising an antibody include, for example, peptide portions of the N-terminal 85 amino acids or the BAG domain of any of the human BAG

proteins (see Figure 1B). A particularly advantageous use of such a protein is for the immunostaining, wherein the methods provides a process to contrast the immunostaining of BAG-family proteins in carcinoma cells with adjacent non-neoplastic prostatic epithelial and basal cells which are generally present in the same tissue sections. These results would be correlated with a Gleason grade to determine whether any of the BAG-family proteins tend to be expressed at higher or lower levels in histologically advanced tumors. From this process a determination can be made as to degree at which the disease is progressing in a given patient, i.e., a prognosis can be made.

Non-immunogenic fragments or synthetic peptides of BAG proteins can be made immunogenic by coupling the hapten to a carrier molecule such bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH), as described in Example IV, below. In addition, various other carrier molecules and methods for coupling a hapten to a carrier molecule are well known in the art and described, for example, by Harlow and Lane, *Antibodies: A laboratory manual* (Cold Spring Harbor Laboratory Press, 1988), which is incorporated herein by reference.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE I

Isolation and Characterization of BAG-family cDNA Sequences

This example describes methods for isolating and characterizing of BAG-family cDNA sequences from human, nematode and yeast.

A. Cloning of human BAG cDNA sequences

Yeast two-hybrid library screening of a human Jurkat cell cDNA library was performed as described by Takayama et al., EMBO J., 16:4887-96 (1997); Matsuzawa et al., EMBO J., 17:2736-2747 (1998), which are incorporated herein by reference) using EGY48 strain yeast transformed with pGilda-Hsc70/ATPase (67-377 amino acids) and the *lacZ* reporter plasmid pSH18-34. Of the resulting ~5 x 10^6 transformants, 112 Leu^+ colonies were obtained after 1 week incubation at 30°C. Assay of β-galactosidase (β-gal) activity of these colonies resulted in 96 clones. Mating tests were then performed using RFY206 yeast strain transformed with pGilda, pGilda mBAG-1 (1-219), or pGilda Hsc70/ATPase. Of these, 66 displayed specific interactions with Hsc70/ATPase. The pJG4-5 cDNAs were recovered using KC8 *E. coli* strain which is auxotrophic for tryptophan (Trp). DNA sequencing revealed 3 partially overlapping human BAG-1, 4 identical and one overlapping cDNAs encoding BAG-2, and 2 partially overlapping BAG-3 clones.

Using the above described yeast two-hybrid screen with the ATPase domain of Hsc70 as "bait", several human cDNAs were cloned which encode portions of BAG-1 or of two other BAG-1-like proteins which are termed BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6). The longest of the cDNAs for BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) contained open reading frames (ORFs) of 207 and 162 amino acids, respectively, followed by stop codons. All BAG-1 (SEQ ID

NO:1), BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) cDNAs obtained by two-hybrid library screening with Hsc70/ATPase contained a conserved domain of about 40-50 amino acids which are termed the "BAG" domain and are shown in Figure 10. These results demonstrate that a family of BAG-1-related proteins all contain a conserved ~45 amino acid region near their C-terminus that binds Hsc70/Hsp70.

B. Identification of additional BAG-family proteins

A search of the translated Genbank database using the bBLAST and FASTA search programs also identified human ESTs that provided sequences for further investigation of BAG-family proteins. The putative BAG-4 (SEQ ID NO:8) and BAG-5 (SEQ ID NO:10) proteins contain BAG-domains that share the greatest sequence similarity with the BAG-domain of BAG-3 (SEQ ID NO:6). These were designated BAG-4 (Accession number AA693697, N74588) and BAG-5 (Accession number AA456862, N34101). BAG-4 has 62% identity and ~81% similarity to BAG-3, and BAG-5 has 51% identity and ~75% similarity to BAG-3.

Additional BAG-family orthologues or homologues were also identified using computer-based searches and resulted in BAG-family homologue in the nematode *C. elegans* and the fission yeast *S. pombe*. The *C. elegans* genome encodes two apparent BAG-family proteins, which are most similar in their overall sequences to the human BAG-1 (Afo39713, gi:2773211) (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14) (Afo68719, gi:3168927). The *S. pombe* contains two BAG-family proteins that share the greatest overall sequence similarity with human BAG-1 (Alo23S54,gi/3133105 and Alo23634, gi/3150250). The human and *C. elegans* BAG-1 proteins as well as *S. pombe* BAG-1A all have ubiquitin-like domains near their N-termini (see Figure 10A) of unknown function.

The overall predicted amino acid sequences of the *C. elegans* BAG-1 (SEQ ID NO:12) and *S. pombe* BAG-1A (SEQ ID NO:16) proteins are ~18% identical (~61% similar) and ~17% identical (~64% similar), respectively, to human BAG-1, implying origin from a common ancestral gene. The *C. elegans* BAG-1 protein (SEQ ID NO:12), however, contains a 5 to 7 amino acid insert in its BAG-domain as compared to the human, murine, and yeast BAG-1 homologues (see Figure 10B), and is more similar to BAG-2 (SEQ ID NO:4) in regard to its BAG-domain. *C. elegans* and human BAG-2 also may be derived from a common ancestor as the C-terminal 225 amino acid region which encompasses both the BAG domain and upstream region of both *C. elegans* and human BAG-2 share ~34% amino acid sequence identity and ~70% similarity. The human BAG-2 protein (SEQ ID NO:4), however, contains a 9 amino acid insert in its BAG-domain compared to it *C.elegans* counterpart (see Figure 10B). Evolutionary-tree prediction algorithms suggest that human and *C. elegans* BAG-2 represent a distinct branch of the BAG-family that is more evolutionarily distant from the other BAG-family proteins. None of the predicted BAG-family proteins contain recognizable regions analogous to those found in other Hsc70 regulatory proteins, such as the J-domains and G/F-domains of DnaJ family proteins and the Tetratricopeptide Repeat (TR) domains of Hip/Hop family proteins.

C. Yeast two-hybrid assay of BAG binding to Hsc70/ATPase

The longest of the cDNAs obtained for the BAG-2 and BAG-3 proteins were expressed with N-terminal transactivation (TA) domains in yeast and tested by yeast two-hybrid assay for interactions with fusion proteins consisting of Hsp70/ATPase or a variety of unrelated proteins (Fas, Siah, Fadd) containing N-terminal LexA DNA-binding domains. TA-BAG-2 and TA-BAG-3 demonstrated

positive interactions with LexA-Hsc70/ATPase, resulting in transactivation of a *lacZ* reporter gene that was under the control of LexA operators (Figure 11A). No interactions with LexA-Fas (cytosolic domain), LexA-Siah, LexA-Fadd, or LexA were detected (see Figure 11A) demonstrating that the BAG-2 and BAG-3 proteins interact specifically with Hsc70/ATPase. Specific two-hybrid interactions between Hsc70/ATPase and either BAG-2 or BAG-3 were also observed when BAG-2 and BAG-3 were expressed as LexA DNA-binding domain fusion proteins and Hsc70/ATPase was fused with a TA domain (see Figure 11A; right panel). These results demonstrate that similarly to BAG-1, BAG-2 and BAG-3 specifically interact with Hsc70/ATPase.

In order to determine whether the BAG proteins are capable of forming heterodimers, coexpression of BAG-2 and BAG-3 in the yeast two-hybrid assay was also performed. Coexpression of BAG-2 and BAG-3 failed to show interaction with BAG-1 or a deletion mutant of BAG-1 (ΔC) which is missing part of its C-terminal domain required for Hsp70/Hsc70 binding suggest that these proteins do not form heterdimers.

D. Isolation and characterization of the complete open reading frame sequences of BAG-2 and BAG-3

In order to deduce the complete ORFs of BAG-2 and BAG-3, a λ-phage cDNA library was screened as follows, using hybridization probes derived from the two-hybrid screening. A human jurkat T-cell λ-ZapII library cDNA library (Stratagene) was screened by hybridization using ^{32}P-labeled purified insert DNA from the longest of the human BAG-2 (clone #11) and human BAG-3 (clone #28) cDNA clones. From about one million clones screened, 38 BAG-2 and 23 BAG-3 clones were identified, cloned, and their cDNA inserts recovered as pSKII plasmids using a helper phage method (Stratagene). DNA sequencing of λ-phage derived

human BAG-2 cDNA clones revealed an ORF encoding a predicted 211 amino acid protein, preceded by an in-frame stop codon. The longest human BAG-3 λ-phage cDNA clone contains a continuous ORF of 682 amino acids followed by a stop codon, but without an identifiable start codon (see Figure 10A).

Although BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) all contain a homologous BAG domain near their C-terminus, the N-terminal regions of these proteins are dissimilar. Using a combination of search tools (Prosite Search: PP search, using the Prosite pattern database, BCM Search Launcher, Baylor College of Medicine, and Blocks Search), it was determined that the BAG-2 N-terminal region contains potential kinase phosphorylation sites but otherwise shares no apparent similarity with other proteins or known functional domains.

In contrast, the predicted N-terminal region BAG-3 contains a WW domain as shown in Figure 10A. WW domains have been identified in a wide variety of signaling proteins, including a Yes kinase adaptor protein (YAP), the Na^{+}-channel regulator Nedd4, formin-binding proteins, dystrophin, and the peptidyl prolyl cis-trans-isomerase Pin-1. These roughly 40 amino acid domains mediate protein interactions and bind the preferred peptide ligand sequence xPPxY (Sudol., TIBS, 21: 161-163, 1996, which is incorporated herein by reference).

EXAMPLE II

In vitro Association of BAG proteins and Hsc70/ATPase

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) bind Hsc70/ATPase in various *in vitro* assays.

A. Solution binding assay of BAG-2 and BAG-3 to Hsc70/ATPase

Association of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) with Hsc70/ATPase was determine by an *in vitro* protein binding assay where Hsc70/ATPase or BAG-family proteins were expressed in bacteria as Glutathione S-Transferase (GST) fusion proteins. Purified cDNA sequences encoding residues 5 to 211 of human BAG-2 (clone #11) and the C-terminal 135 amino acids of human BAG-3 (clone #28) (see Figure 10A) were subcloned into the EcoRI/Xho I sites of pGEX4T-1 prokaryotic expression plasmid (Pharmacia; Piscataway, NJ). These plasmids as well as pGEX4T-1-BAG-1, pGEX-4T-1-BAG-1 (ΔC), and pGEX-4T-1-XL which have been described previously (Takayama et al., *supra* (1997); Xie et al., Biochemistry, 37:6410-6418, (1998), which are incorporated herein by reference), were expressed in XL-1 blue strain *E. Coli* (Stratagene, Inc., La Jolla, CA). Briefly, a single colony was inoculated into 1L of LB media containing 50 μg/ml ampicillin and grown at 37°C overnight. The culture was then diluted by half with fresh LB/ampicillin and cooled to room temperature for 1 hr, before inducing with 0.4mM IPTG for 6 h at 25°C.

Cells were recovered and incubated with 0.5 mg/ml lysozyme in 50 mM Tris (pH 8.0), 150 mM NaCl, 1% Tween-20, 0.1% 2-mercaptoethanol, 5 mM EDTA, 1 mM PMSF and a mixture

of other protease inhibitors obtained from Boehringer Mannheim (1697498) at room temperature for 0.5 h, followed by sonication. Cellular debris were pelleted by centrifugation at 27,500g for 10 min and the resulting supernatants were incubated with 30 ml of glutathionine-Sepharose (Pharmacia) at 4°C overnight. The resin was then washed with 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, and 0.1% 2-mercaptoethanol until the OD 280nm reached <0.01. For removal of GST, the resin with immobilized GST-fusion protein was incubated with 10U of thrombin (Boehringer, Inc.) at 4°C in 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, 0.1% 2-Mercaptoethanol, and 2.5 mM CaCl2 overnight. Released proteins were then purified on Mono Q (HR10/10, Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0 and dialyzed into chaperone assay buffer.

The ability of BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) to bind Hsc70/ATPase in solution was then examined. GST control or GST-BAG proteins were immobilized on glutathione-Sepharose and tested for binding to 35S-labeled *in vitro* translated (IVT) proteins. Immunoprecipitation and *in vitro* GST-protein binding assays were performed as described by Takayama et al., *supra* (1997), using pCI-Neo flag or pcDNA3-HA into which human Bag-2 (clone #11) or human BAG-3 (clone #28) had been subcloned for *in vitro* translation of 35S-L-methionine labeled proteins or expression in 293T cells. As shown in Figure 11B, ^{35}S-Hsc70/ATPase bound *in vitro* to GST-BAG-1, GST-BAG-2, and GST-BAG-3 but not to GST-BAG-1(ΔC) or several other control proteins. BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) also exhibited little or no binding to themselves or to each other, demonstrating that these proteins do not strongly homo- or hetero-dimerize or oligomerize. It should be noted, however, that BAG-2 (SEQ

ID NO:4) displayed weak interactions with itself in binding assays and produced a positive result in yeast two-hybrid experiments, demonstrating that it can have the ability to self-associate.

B. Binding of BAG proteins to Hsc70 *in vivo*

The ability of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins to interact in cells with Hsc70 was tested by expressing these proteins with N-terminal Flag epitope tags in 293T human epithelial cells using co-immunoprecipitation assays as described previously (Takayama et al., *supra* (1997)). cDNAs encoding the λ-phage cloned regions of BAG-2 and BAG-3 were subcloned in-frame into pcDNA3-Flag. Anti-Flag immune complexes prepared from 293T cells after transfection with plasmids encoding Flag-BAG-1, Flag-BAG-2, or Flag-BAG-3 were analyzed by SDS-PAGE/immunoblot assay. As shown in Figure 10C, antiserum specific to Hsc70 detected the presence of BAG proteins associated with Hsc70, whereas control immune-complexes prepared with IgG1 as well as anti-Flag immune complexes prepared from cells transfected with Flag-tagged control proteins, Daxx and Apaf-1, did not contain Hsc70 associated protein. These results further demonstrate that BAG-family proteins specifically bind to Hsc70.

C. BIAcore assay of BAG protein binding to the ATPase domain of Hsc70

BAG-1 (beginning at residue 116 of SEQ ID NO:2) is known to bind tightly to the ATPase domain of Hsc70 (Stuart et al., J. Biol. Chem., In Press (1998)). BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins were therefore, examined for their ability to bind to Hsc70/ATPase. The affinity and binding kinetics of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) to Hsc70/ATPase was also compared to that of BAG-1 (beginning at residue 116 of

SEQ ID NO:2) for Hsc70/ATPase, using a surface plasmon resonance technique (BIAcore) which has been described previously (Stuart et al., *supra,* (1998) which is incorporated herein by reference).

BAG-family proteins were produced in bacteria and purified to near homogeneity as shown in Figure 12A and described above in Example I. The purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), -2 (SEQ ID NO:4), and -3 (SEQ ID NO:6) proteins were then immobilized on biosensor chips and tested for their interactions with Hsc70 in the soluble phase. Kinetic measurements were performed using a BIAcore-II instrument with CM5 sensor chip and Amine Coupling Kit (Pharmacia Biosensor AB, Sweden). Briefly, for immobilization of proteins, the sensor chip was equilibrated with HK buffer (10 mM Hepes (pH 7.4), 150 mM KCL) at 5μl/min, then activated by injecting 17 μl of 0.2M N-ethyl-N'-(3-diethylaminopropyl)-carbodiimide and 0.05M N-hydroxysuccinimide (NHS/EDC) followed by 35 μl of the protein of interest, in 10 mM acetate, pH 3.5-4.5. Excess NHS-ester on the surface was deactivated with 17 μl 1M ethanolamine-HCL (pH8.5). After immobilization, 5μl of regeneration buffer (50 mM phosphate (pH 6.8) and 4M GuHCl) was injected. For binding assays, Hsp70 (Sigma, H8778) was dissolved in HK buffer, and injected at 10 μl/min across the prepared surface at various concentrations. The surface was regenerated after each injection with 5 μl of regeneration buffer. The rate constants κ_{ass} and κ_{diss} were generated with BIAevaluation softward 3.01 (Pharmacia Biosensor AB). Addition of Hsc70 to chips containing BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) resulted in concentration-dependent binding, as reflected by an increase in the Response Units (RU) measured at the chip surface (shown in Figure 3B). In contrast, Hsc70 failed to display interactions in BIAcore assays with a variety of control proteins as well as a mutant of BAG-1

lacking a C-terminal portion of the BAG domain which is required for Hsc70-binding (Figure 3B). Furthermore, flowing of various control proteins such as GST, BSA and Bcl-XL over the BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) chips resulted in negligible interaction. These results further demonstrate the specificity with which BAG-family proteins interact with and bind to Hsc70.

The rates of Hsc70 binding to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) proteins were similar, following pseudo first-order kinetics with estimated association rate constants (κ_a) of 2.1, 2.1 and 2.4 x 10^5 M^{-1} sec^{-1}, respectively. After allowing binding of Hsc70 to immobilized BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to reach plateau levels, the chaperone was removed from the flow solution and the dissociation rate was monitored. BAG-1 (beginning at residue 116 at SEQ ID NO:2) and BAG-2 (SEQ ID NO:4) exhibited similar dissociation rates, with relatively slow loss of Hsc70 from the chip surface, resulting in estimated dissociation rate constants (κ_d) of 3.0 and 5.0 x 10^{-4} sec^{-1}, respectively (see Figure 3B). In contrast, Hsc70 dissociated more rapidly from biosensor chips containing BAG-3 (see Figure 3B), yielding an estimated κ_d of 1.7 x 10^{-3} sec^{-1}. From the kinetic data, the apparent affinities ($\kappa_D = \kappa_d/\kappa_a$) were calculated for binding of Hsc70 to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) and were estimated to equal about K_D= 1.4nM, K_D=2.4nM, and K_D=7.4nM, respectively. These results demonstrate that the interactions of BAG-family proteins with Hsc70 occur with apparent affinities sufficient for physiological relevance.

EXAMPLE III

BAG-family proteins inhibit Hsp70/Hsc70-dependent protein folding

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins inhibit Hsp70/Hsc70-dependent refolding of denatured proteins similarly to a BAG-1 (beginning at residue 116 of SEQ ID NO:2) protein.

The effects of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) protein on Hsp70/Hsc70-dependent protein refolding was determined using *in vitro* protein refolding assays similar to those described previously by Takayama et al., *supra*, 1998; Terada et al., J Cell Biol., 139:1089-1095, 1997, which are incorporated herein by reference. Briefly, luciferase (20μM) was denatured in 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT, 6M guanidine hydrochloride at ~25°C for 1 h. Denatured luciferase was diluted 1:40 into 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT. Hsc70 (1.8 μM), DnaJ (StressGen, Inc.) (0.9μM), and various purified recombinant proteins as indicated were added to refolding buffer (30 mM Hepes-KOH, pH 7.6, 120 mM potassium acetate, 3mM magnesium acetate, 2 mM DTT, 2.5 mM ATP) with 0.2 volume of diluted denatured luciferase to a final concentration of 0.1 μM. Luciferase activity was measured after 1.5 hr incubation at 35°C.

The combination of Hsc70 and DnaJ resulted in ATP-dependent refolding of chemically denatured firefly luciferase, with function of over half the denatured enzyme restored in a 90 minute reaction, as monitored by a chemiluminescence assay. In contrast, neither Hsc70 nor DnaJ alone were able to induce substantial refolding of denatured luciferase. Furthermore, little spontaneous

restoration of luciferase activity was observed with control proteins, BSA, GST or Bcl-XL (see Figure 4A).

Addition of recombinant purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to the above assays in amounts equimolar to Hsc70 (1.8 μM) resulted in striking inhibition of luciferase refolding. BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) displayed somewhat greater inhibitory activity than BAG-1 (beginning at residue 116 of SEQ ID NO:2) as shown in Figure 4A. In contrast, the BAG-1 (ΔC) protein, which fails to bind Hsc70 as well as several other control proteins, had no effect on luciferase refolding.

In an additional refolding assay, described previously by Minami et al., J Biol. Chem. 271:19617-24, 1996), purified Hsc70 and human DnaJ homolog Hdj-1 (Hsp 40) were used with additional cofactors provided in reticulocyte lysates (5% v:v) to produce a system capable of refolding denatured luciferase. Briefly, additional cofactors included, recombinant Luciferase (Promega: QuantiLum TM), that had been heat denatured at 42°C for 10 min, 1.8 μM Hsc70 (Sigma; purified from bovine brain), 0.9 μM Hsp40, and various recombinant purified proteins. Luciferase activity was measured (Promega luciferase assay kit) using a luminometer (EG&G Berthold, MicroLumat luminometer, Model #LB96P). All results were normalized relative to non-denatured luciferase that had been subjected to the same conditions. Control reactions lacking ATP, Hsc70, or Hsp40 resulted in negligible luciferase refolding.

Various amounts of purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6), relative to amounts of Hsc70 were used in the above-described protein refolding assay. Addition of BAG-family proteins resulted in a concentration-dependent

inhibition of Hsc70 chaperone activity. Furthermore, the BAG-2 (SEQ ID NO:4)and BAG-3 (SEQ ID NO:6) inhibition of Hsc70 chaperone activity was demonstrated to be as potent as that observed for BAG-1 (beginning at residue 116 of SEQ ID NO:2). In contrast, the BAG-1 (ΔC) mutant as well as other control proteins did not suppress Hsc70-mediated refolding of denatured luciferase. These results indicate that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) can inhibit Hsc70/Hsp70 dependent protein refolding activity to the same extent as BAG-1 (beginning at residue 116 of SEQ ID NO:2).

B. BAG competes with Hip for binding to Hsc70.

It is known that BAG-1 competes with Hip for binding to Hsc70, with these proteins exerting opposite effects on Hsc70-mediated protein refolding (Hohfeld, J., and Jentsch, S., *Embo J.*, 16:6209-6216, 1997, which is incorporated herein by reference). In order to determine whether BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) also compete with Hip for binding to Hsc70, refolding assays were performed as described above in the presence of Hip protein.

Hip was purified as His_6-protein. The fusion protein was induced from pET28-Hip (V. Prapapanich et al., *Mol Cell Biol.*, 18:944-952, 1998, which is incorporated herein by reference) with 0.1 mM IPTG at 25°C for 6h in BL21 cells. Cells from 1L of culture were resuspended into 50 ml of 50 mM Phosphate buffer (pH 6.8), 150 mM NaCl, and 1% (v/v) Tween-20 and then incubated with 0.5 mg/ml lysozyme at 25°C for 0.5h, followed by sonication. After centrifugation at 27,500g for 10 min, the resulting supernatant was mixed with 15 ml nickel resin (Qiagen, Inc.) at 4°C for 3 h with 25 mM imidazol. The resin was then washed with 50 mM phosphate buffer (pH 6.8), 25 mM imidazol, 150 mM NaCl and 0.1% Tween-20 until the OD280nm

reached a value of <0.01. His_6-Hip protein was eluted with 250 mM imidazol in washing buffer (Qiagene, Inc.) and purified on Mono Q (HR10/10 Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0, followed by dialysis in chaperone assay buffer.

In the refolding assay reactions, addition of purified Hip at equimolar concentrations relative to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) (1.8 μM) completely negated the inhibitory effects of the BAG-family proteins on refolding of denatured luciferase (see Figure 4C). These results demonstrate that the suppression of Hsc70 chaperone activity by BAG-family proteins is reversible, and that Hip antagonizes the effects of not only BAG-1 (beginning at residue 116 of SEQ ID NO:2), but also of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6).

In summary, these results demonstrate that BAG-family proteins all contain a conserved BAG domain near their C-terminus that binds Hsc70/Hsp70, and that human BAG-family proteins can bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity through a Hip-repressable mechanism.

EXAMPLE IV

EXPANDED NUCLEIC ACID AND AMINO ACID SEQUENCES FOR HUMAN BAG-3, BAG-4 AND BAG-5

Following the procedures disclosed herein, the nucleic acid and amino acids sequences to human BAG-3, BAG-4 and BAG-5 were further expanded. The expanded sequences for BAG-3, BAG-4 and BAG-5 are shown in Figures 15, 16 and 17, respectively, with their respective sequence identification numbers, "SEQ ID NO"s.

We claim:

1. A compound of the formula,

$$R^N\text{-}R^1X^1R^2X^2R^3X^3R^4X^4R^5X^5R^6X^6R^7X^7X^8R^9X^9R^{10}X^{10}R^{11}X^{11}\text{-}R^C$$

wherein,

R^N is a group of about 1 to 552 independently selected amino acids;

R^1 is a group of 3 independently selected amino acids;

X^1 is an amino acid with a charged or uncharged R group;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group;

X^8 is an amino acid with a charged R group;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group;

R^{10} is a group of 3 independently selected amino acids;

X^{10} is an amino acid with an uncharged R group;

R^{11} is a group of 2 independently selected amino acids;

X^{11} is an amino acid with an apolar R group; and

R^{C} is a group of about 1 to 100 independently selected amino acids.

2. A substantially purified nucleic acid molecule having a nucleotide sequence corresponding to or complementary to at least 20 nucleotides from a nucleotide sequence selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

3. The nucleic acid of claim 2 having a nucleotide sequence corresponding to or complementary to a nucleotide sequence that encodes a functionally active BAG family protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

4. The nucleic acid of claim 3 selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

5. The nucleic acid of claim 3 complementary to a nucleotide sequence that encodes a functionally active BAG protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

6. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:3).

7. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:5).

8. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:7).

9. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:9).

10. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:19).

11. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:21).

12. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:23).

13. A substantially purified BAG family protein encoded by the nucleic acid molecule of claim 1.

14. A substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24) or a fragment, a derivative or a mimetic thereof.

15. A substantially purified protein corresponding to the amino acid sequence of 157 to 204 of (SEQ ID NO:2).

16. A substantially purified protein corresponding to the amino acid sequence of 272 to 319 of (SEQ ID NO:2).

17. A substantially purified protein corresponding to the amino acid sequence of 164 to 211 of (SEQ ID NO:4).

18. A substantially purified protein corresponding to the amino acid sequence of 418 to 510 of (SEQ ID NO:20).

19. A substantially purified protein corresponding to the amino acid sequence of 378 to 457 of (SEQ ID NO:22).

20. A substantially purified protein corresponding to the amino acid sequence of 6 to 97 of (SEQ ID NO:24).

21. A substantially purified protein corresponding to the amino acid sequence of 180 to 257 of (SEQ ID NO:24).

22. A substantially purified protein corresponding to the amino acid sequence of 272 to 349 of (SEQ ID NO:24).

23. A substantially purified protein corresponding to the amino acid sequence of 362 to 444 of (SEQ ID NO:24).

24. A pharmaceutical composition comprising a nucleic acid molecule of claim 1 useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

25. A method of modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function by administering a nucleic acid molecule of claim 1.

26. A pharmaceutical composition comprising a substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24), or a fragment, a derivative or a mimetic thereof, useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

27. A method of modulating tumor cell proliferation by administering a pharmaceutical composition of claim 26.

28. A method of modulating cell migration and metastasis by administering a pharmaceutical composition of claim 26.

29. A method of modulating steroid hormone receptor function by administering a pharmaceutical composition of claim 26.

30. A substantially purified antibody that specifically binds to a BAG family protein of claim 14.

31. The antibody of claim 30, wherein said antibody is a monoclonal antibody.

32. A method for detecting the presence of a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said an antibody of claim 11 under suitable conditions for the binding of said antibody with the BAG family protein; and

c. detecting said bound BAG family protein.

33. A method for detecting the presence of a first nucleic acid molecule that encodes a BAG family protein in a sample, comprising the steps of:

a. obtaining the sample;

b. adding to said sample a second nucleic acid molecule capable of hybridizing with said first nucleic acid molecule under suitable conditions for the binding of said second nucleic acid molecule with said first nucleic acid molecule; and

c. detecting said hybridized first and second nucleic acid molecules.

34. A method of determining the risk of metastatic spread of cancer or prognosis of cancer patients by determining the level of expression of a BAG-family protein.

FIGURE 1

```
ACGCCGCGCT CAGCTTCCAT CGCTGGCCGG TCAACAAGTG CGGGCCTGGC TCAGCGCGGG GCGGCGCCGA GACCGCGAGG CGACCCGGAG    90
                                                   L A   Q R G   G A R R   P R G   D R E
                                                   BAG-1L
CGGCTGGGTT CCCGGCTGCG CGCCCTTCGG CCAGGCCCGG AGCCGCGCCA GTCGGAGCCC CCGGCCCAGC GTGGTCCGCC TCCCTCTCGG   180
R L G S    R L R    A L R    P G R E    P R Q    S E P    P A Q R    G P P    P S R

CGTCCACCTG CCCGGAGTAC TGCCAGCGGG CATGACCGAC CCACCAGGGG CGCCGCCGCC GGCGCTCGCA GGCCGCGGAT GAAGAAGAAA   270
R P P A    R S T    A S G    H D R P    T R G    A A A    G A R R    P R M    K K K
                                                                                      BAG-1M
ACCCGGCGCC GCTCGACCCG GAGCGAGGAG TTGACCCGGA GCGAGGAGTT GACCCTGAGT GAGGAAGCGA CCTGGAGTGA AGAGGCGACC   360
T R R R    S T R    S E E    L T R S    E E L    T L S    E E A T    W S E    E A T

CAGAGTGAGG AGGCGACCCA GGGCGAAGAG ATGAATCGGA GCCAGGAGGT GACCCGGGAC GAGGAGTCGA CCCGGAGCGA GGAGGTGACC   450
Q S E E    A T Q    G E E    M N R S    Q E V    T R D    E E S T    R S E    E V T
                              BAG-1
AGGGAGGAAA TGGCGGCAGC TGGGCTCACC GTGACTGTCA CCCACAGCAA TGAGAAGCAC GACCTTCATG TTACCTCCCA GCAGGGCAGC   540
R E E M    A A A    G L T    V T V T    H S N    E K H    D L H V    T S Q    Q G S

AGTGAACCAG TTGTCCAAGA CCTGGCCCAG GTTGTTGAAG AGGTCATAGG GGTTCCACAG TCTTTTCAGA AACTCATATT TAAGGGAAAA   630
S E P V    V Q D    L A Q    V V E E    V I G    V P Q    S F Q K    L I F    K G K

TCTCTGAAGG AAATGGAAAC ACCGTTGTCA GCACTTGGAA TACAAGATGG TTGCCGGGTC ATGTTAATTG GGAAAAAGAA CAGTCCACAG   720
S L K E    M E T    P L S    A L G I    Q D G    C R V    M L I G    K K N    S P Q

GAAGAGGTTG AACTAAAGAA GTTGAAACAT TTGGAGAAGT CTGTGGAGAA GATAGCTGAC CAGCTGGAAG AGTTGAATAA AGAGCTTACT   810
E E V E    L K K    L K H    L E K S    V E K    I A D    Q L E E    L N K    E L T

GGAATCCAGC AGGGTTTTCT GCCCAAGGAT TTGCAAGCTG AAGCTCTCTG CAAACTTGAT AGGAGAGTAA AAGCCACAAT AGAGCAGTTT   900
G I Q Q    G F L    P K D    L Q A E    A L C    K L D    R R V K    A T I    E Q F

ATGAAGATCT TGGAGGAGAT TGACACACTG ATCCTGCCAG AAAATTTCAA AGACAGTAGA TTGAAAAGGA AAGGCTTGGT AAAAAAGGTT   990
M K I L    E E I    D T L    I L P E    N F K    D S R    L K R K    G L V    K K V

CAGGCATTCC TAGCCGAGTG TGACACAGTG GAGCAGAACA TCTGCCAGGA GACTGAGCGG CTGCAGTCTA CAAACTTTGC CCTGGCCGAG  1080
Q A F L    A E C    D T V    E Q N I    C Q E    T E R    L Q S T    N F A    L A E

TGAGGTGTAG CAGAAAAAGG CTGTGCTGCC CTGAAGAATG GCGCCACCAG CTCTGCCGTC TCTGGATCGG AATTTACCTG ATTTCTTCAG  1170

GGCTGCTGGG GGCAACTGGC CATTTGCCAA TTTTCCTACT CTCACACTGG TTCTCAATGA AAAATAGTGT CTTTGTGATT TGAGTAAAGC  1260

TCCTATTCTG TTTTTCACAA AAAAAAAAAA A                                                                 1291
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FIGURE 2A

```
GCAGCCGCGG TGTCGCGAAG TCCTCCCGGG TTGCCCCCGC GGCGTCAGAG GGAGGGCGGG CGCCGCGTTG GTGACGGCGA CCCTGCAGCC   90
CAAGGAGCGC TCCACTCGCT GCCGCCGGAG GGCCGGTGAC CTCTTGGCTA CCCCGCGTCG GAGGCTTAGA TGGCTCAGGC GAAGATCAAC  180
                                                                   .  M    A  Q  A   K  I  N

GCTAAAGCCA ACGAGGGGCG CTTCTGCCGC TCCTCCTCCA TGGCTGACCG CTCCAGCCGC CTGCTGGAGA GCCTGGACCA GCTGGAGCTC  270
A  K  A  N    E  G  R   F  C  R   S  S  S  M    A  D  R   S  S  R   L  L  E  S    L  D  Q   L  E  L

AGGGTTGAAG CTTTGAGAGA AGCAGCAACT GCTGTTGAGC AAGAGAAAGA AATCCTTCTG GAAATGATCC ACAGTATCCA AAATAGCCAG  360
R  V  E  A    L  R  E   A  A  T   A  V  E  Q    E  K  E   I  L  L   E  M  I  H    S  I  Q   N  S  Q

GACATGAGGC AGATCAGTGA CGGAGAAAGA GAAGAATTAA ATCTGACTGC AAACCGTTTG ATGGGAAGAA CTCTCACCGT TGAAGTGTCA  450
D  M  R  Q    I  S  D   G  E  R   E  E  L  N    L  T  A   N  R  L   M  G  R  T    L  T  V   E  V  S

GTAGAAACAA TTAGAAACCC CCAGCAGCAA GAATCCCTAA AGCATGCCAC AAGGATTATT GATGAGGTGG TCAATAAGTT TCTGGATGAT  540
V  E  T  I    R  N  P   Q  Q  Q   E  S  L  K    H  A  T   R  I  I   D  E  V  V    N  K  F   L  D  D

TTGGGAAATG CCAAGAGTCA TTTAATGTCG CTCTACAGTG CATGTTCATC TGAGGTGCCA CATGGGCCAG TTGATCAGAA GTTTCAATCC  630
L  G  N  A    K  S  H   L  M  S   L  Y  S  A    C  S  S   E  V  P   H  G  P  V    D  Q  K   F  Q  S

ATAGTAATTG GCTGTGCTCT TGAAGATCAG AAGAAAATTA AGAGAAGATT AGAGACTCTG CTTAGAAATA TTGAAAACTC TGACAAGGCC  720
I  V  I  G    C  A  L   E  D  Q   K  K  I  K    R  R  L   E  T  L   L  R  N  I    E  N  S   D  K  A

ATCAAGCTAT TAGAGCATTC TAAAGGAGCT GGTTCCAAAA CTCTGCAACA AAATGCTGAA AGCAGATTCA ATTAGTCTTC AAACCTAAGA  810
I  K  L  L    E  H  S   K  G  A   G  S  K  T    L  Q  Q   N  A  E   S  R  F  N
```

FIGURE 2B

```
GCATTTACAC AATACACAAG GTGTAAAAAT GATAAAATAC TATTTTAATT GATAACTAGT TCTTTGTTAG GTATAACCAC TTAGTTGACA    900
CTGATAGTTG TTTCAGATGA GGAAAATATT CCATCAAGTA TCTTCAGTTT TGTGAATAAC AAAACTAGCA ATATTTTAAT TATCTATCTA    990
GAGATTTTTT AGATTGAATT CTTGTCTTGT ACTAGGATCT AGCATATTTC ACTATTCTGT GGATGAATAC ATAGTTTGTG GGGAAAACAA   1080
ACGTTCAGCT AGGGGCAAAA AGCATGACTG CTTTTTCCTG TCTGGCATGG AATCACGCAG TCACCTTGGG CATTTAGTTT ACTAGAAATT   1170
CTTTACTGG                                                                                            1179
```

FIGURE 3

```
GCGGAGCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGGACTGGA CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC    90
A E L R   I Q P   R A A   A N F S   G L D   Q K F   L A G Q   L L P   P F I

TCCTCCTTCC CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC ACGTCACCCC CGCCTTTAAT TCATAAAGGT   180
S S F P   S G S   E E A   I S R H   F H P   S L A   T S P P   P L I   H K G

GCCCGGCGCC GGCTTCCCGG ACACGTCGGC GGCGGAGAGG GGCCCACGGC GGCGGCCCGG CCAGAGACTC GGCGCCCGGA GCCAGCGCCC   270
A R R R   L P G   H V G   G G E G   P T A   A A R   P E T R   R P E   P A P

CGCACCCGCG CCCCAGCGGG CAGACCCCAA CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG CAACGGTGAC   360
R T R A   P A G   R P Q   P S M S   A A T   H S P   M M Q V   A S G   N G D

CGCGACCCTT TGCCCCCCGG ATGGGAGATC AAGATCGACC CGCAGACCGG CTGGCCCTTC TTCGTGGACC ACAACAGCCG CACCACTACG   450
R D P L   P P G   W E I   K I D P   Q T G   W P F   F V D H   N S R   T T T

TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC TGCCAATGGC CCTTCCCGGG AGGGCTCTAG GCTGCCGCCT   540
W N D P   R V P   S E G   P K E T   P S S   A N G   P S R E   G S R   L P P

GCTAGGGAAG GCCACCCTGT GTACCCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG CTCCATGAAG GCGCTGAGAA CCGGCAGGTG   630
A R E G   H P V   Y P Q   L R P G   Y I P   I P V   L H E G   A E N   R Q V

CACCCTTTCC ATGTCTATCC CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC AGAGGTCCCA GTCACCTCTG   720
H P F H   V Y P   Q P G   M Q R F   R T E   A A A   A A P Q   R S Q   S P L

CGGGGCATGC CAGAAACCAC TCAGCCAGAT AAACAGTGTG GACAGGTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC CCACGGACCT   810
R G M P   E T T   Q P D   K Q C G   Q V A   A A A   A A Q P   P A S   H G P

GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT   900
E R S Q   S P A   A S D   C S S S   S S S   A S L   P S S G   R S S   L G S

CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC   990
H Q L P   R G Y   I S I   P V I H   E Q N   V T R   P A A Q   P S F   H K A

CAGAAGACGC ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC AAGATCCAGG GGGATGACTG GGAGCCCCGG  1080
Q K T H   Y P A   Q R G   E Y Q T   H Q P   V Y H   K I Q G   D D W   E P R

CCCCTGCGGG CGGCATCCCC GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGGGC TCACCAGCCA GGAGCAGCAC GCCACTCCAC  1170
P L R A   A S P   F R S   S V Q G   A S S   R E G   S P A R   S S T   P L H

TCCCCCTCGC CCATCCGTGT GCACACCGTG GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC CCAGCCTGAA  1260
S P S P   I R V   H T V   V D R P   Q Q P   M T H   R E T A   P V S   Q P E

AACAAACCAG AAAGTAAGCC AGGCCCAGTT GGACCAGAAC TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT  1350
N K P E   S K P   G P V   G P E L   P P G   H I P   I Q V I   R K E   V D S

AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT  1440
K P V S   Q K P   P P P   S E K V   E V K   V P P   A P V P   C P P   P S P


GGCCCTTCTG CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC AGCACTGCCC CTGCAGAAGC TACACCTCCA  1530
G P S A   V P S   S P K   S V A T   E E R   A A P   S T A P   A E A   T P P

AAACCAGGAG AAGCCGAGGC TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG TGCAGGGGCT GGAGCAGGCT  1620
K P G E   A E A   P P K   H P G V   L K V   E A I   L E K V   Q G L   E Q A

GTAGACAACT TTGAAGGCAA GAAGACTGAC AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT GGATTCAGTG  1710
V D N F   E G K   K T D   K K Y L   M I E   E Y L   T K E L   L A L   D S V

GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC  1800
D P E G   R A D   V R Q   A R R D   G V R   K V Q   T I L E   K L E   Q K A

ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT  1890
I D V P   G Q V   Q V Y   E L Q P   S N L   E A D   Q P L Q   A I M   E M G

GCCGTGGCAG CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG  1980
A V A A   D K G   K K N   A G N A   E D P   H T E   T Q Q P   E A T   A A A

ACTTCAAACC CCAGCAGCAT GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA GTCAGACTCG GAACCGATGT  2070
T S N P   S S M   T D T   P G N P   A A P   .

GTGCTTTAGG GATTTTAGTT GCATGCATTT CAGAGACTTT AGGTCAGTTG GTTTTGATTA GCTGCTTGGT ATGCAGTACT TGGGTGAGGC  2160
AAACACTATA AAGGGCTAAA AGGGAAAATG ATGCTTTTCT TCAATATTCT TACTCTTGTA CAATTAANGA AGTTGCTTGT TGTTTGAGAA  2250
GTTTAACCCC GTTGCTTGTT CTGCAGCCCT GTCNACTTGG GCACCCCCAC CACCTGTTAG CTGTGGTTGT GCACTGTCTT TTGTAGCTCT  2340
GGACTGGAGG GGTAGATGGG GAGTCAATTA CCCATCACAT AAATATGAAA CATTTATCAG AAATGTTGCC ATTTTAATGA GATGATTTTC  2430
TTCATCTCAT AATTAAAATA CCTGACTTTA GAGAGAGTAA AATGTGCCAG GAGCCATAGG AATATCTGTA TGTTGGATGA CTTTAATGCT  2520
ACATTTTN                                                                                          2528
```

FIGURE 4

```
ACGATATCCT GTAAGACCAA GAATTGCAAG GCCAGAGTTT GAATTCTTAT ACAAATGGAG CGTATGGTCC AACATACCCC CCAGGCCCTG   90

GGGCAAATAC TGCCTCATAC TCAGGGGCTT ATTATGCACC TGGTTATACT CAGACCAGTT ACTCCACAGA AGTTCCAAGT ACTTACCGTT  180

CATCTGGCAA CAGCCCAACT CCAGTCTCTC GTTGGATCTA TCCCCAGCAG GACTGTCAAG ACTGAAGCAC CCCCTCTTAA GGGGCAGGTT  270

CCAGGATATC CGCCTTCACA GAACCCTGGA ATGACCCTGC CCCATTATCC TTATGGAGAT GGTAATCGTA GTGTTCCACA ATCACGGCCG  360
                                                         M  E  M   V  I  V   V  F  H  N   H  G  R

ACTGTACGAC CACAAGAAAG ATGCGTGGGC TTCTCCTGGT GCTTATGGAA TGGGTGGCCG TTATCCCTGG CCTTCATCAG CGCCCTCAGC  450
 L  Y  D   H  K  K  D   A  W  A   S  P  G   A  Y  G  M   G  G  R   Y  P  W   P  S  S  A   P  S  A

ACCACCCGGC AATCTCTACA TGACTGAAAG TACTTCACCA TGGCCTAGCA GTGGCTCTCC CCAGTCACCC CCTTCACCCC CAGTCCAGCA  540
 P  P  G   N  L  Y  M   T  E  S   T  S  P   W  P  S  S   G  S  P   Q  S  P   P  S  P  P   V  Q  Q

GCCCAAGGAT TCTTCATACC CCTATAGCCA ATCAGATCAA AGCATGAACC GGCACAACTT TCCTTGCAGT GTCCATCAGT ACGAATCCTC  630
 P  K  D   S  S  Y  P   Y  S  Q   S  D  Q   S  M  N  R   H  N  F   P  C  S   V  H  Q  Y   E  S  S

GGGGACAGTG AACAATGATG ATTCAGATCT TTTGGATTCC CAAGTCCAGT ATAGTGCTGA GCCTCAGCTG TATGGTAATG CCACCAGTGA  720
 G  T  V   N  N  D  D   S  D  L   L  D  S   Q  V  Q  Y   S  A  E   P  Q  L   Y  G  N  A   T  S  D

CCATCCCAAC AATCAAGATC AAAGTAGCAG TCTTCCTGAA GAATGTGTAC CTTCAGATGA AAGTACTCCT CCGAGTATTA AAAAAATCAT  810
 H  P  N   N  Q  D  Q   S  S  S   L  P  E   E  C  V  P   S  D  E   S  T  P   P  S  I  K   K  I  I

ACATGTGCTG GAGAAGGTCC AGTATCTTGA ACAAGAAGTA GAAGAATTTG TAGGAAAAAA GACAGACAAA GCATACTGGC TTCTGGAAGA  900
 H  V  L   E  K  V  Q   Y  L  E   Q  E  V   E  E  F  V   G  K  K   T  D  K   A  Y  W  L   L  E  E

AATGCTAACC AAGGAACTTT TGGAACTGGA TTCAGTTGAA ACTGGGGGCC AGGACTCTGT ACGGCAGGCC AGAAAAGAGG CTGTTTGTAA  990
 M  L  T   K  E  L  L   E  L  D   S  V  E   T  G  G  Q   D  S  V   R  Q  A   R  K  E  A   V  C  K

GATTCAGGCC ATATTGGAAA                                                                             1010
 I  Q  A   I  L  E
```

FIGURE 5

```
GAGAAATAAA AAATGAACTT CTCCAAGCAC AAAACCCTTC TGAATTGTAC CTGAGCTCCA AAACAGAATT GCAGGGTTTA ATTGGACAGT    90
 E  I  K   N  E  L   L  Q  A  Q   N  P  S   E  L  Y   L  S  S  K   T  E  L   Q  G  L   I  G  Q  L
TGGATGAGGT AAGTNTTGAA AAAAACCCCT GCATCCGGGA AGCCAGGAGA AGAGCAGTGA TCGAGGTGCA AACTCTGATC ACATATATTG   180
 D  E  V   S  X  E   K  N  P  C   I  R  E   A  R  R   R  A  V  I   E  V  Q   T  L  I   T  Y  I  D
ACTTGAAGGA GGCCCTTGAG AAAAGAAAGC TGTTTGCTTG TGAGGAGCAC CCATCCCATA AAGCCGTCTG GAACGTCCTT GGAAACTTGT   270
 L  K  E   A  L  E   K  R  K  L   F  A  C   E  E  H   P  S  H  K   A  V  W   N  V  L   G  N  L  S
CTGAGATCCA GGGAGAAGTT CTTTCATTTG ATGGAAATCG AACCGATAAG AACTACATCC GGCTGGAAGA GCTGCTCACC AAGCAGCTGC   360
 E  I  Q   G  E  V   L  S  F  D   G  N  R   T  D  K   N  Y  I  R   L  E  E   L  L  T   K  Q  L  L
TAGCCCTGGA TGCTGTTGAT CCGCAGGGAG AAGAGAAGTG TAAGGCTGCC AGGAAACAAG CTGTGAGGCT TGCGCAGAAT ATTCTCAGCT   450
 A  L  D   A  V  D   P  Q  G  E   E  K  C   K  A  A   R  K  Q  A   V  R  L   A  Q  N   I  L  S  Y
ATCTCGACCT GAAATCTGAT GAATGGGAGT ACTGAAATAC CAGAGATCTC ACTTTTGATA CTGTTTTGCA CTTCATATGT GCTTCTATGT   540
 L  D  L   K  S  D   E  W  E  Y   .
ATAGAGAGCT TTCAGTTCAT TGATTTATAC GTGCATATTT CAGTCTCAGT ATTTATGATT GAAGCAAATT CTATTCAGTA TCTGCTGCTT   630
TTGATGTTGC AAGACAAATA TCATTACAGC ACGTTAACTT TTCCATTCGG ATCAAAAAA                                     689
```

FIGURE 6A

ATGTCTTTCCGCCTCTTCGTTGAAATATTTCACTTTCTTTTCCAGCTTTTTCCCCATCTCGACCT
GCTTTGGTTTTT
CGAGAAAACCACGTTCCAAATCAGCGACATCTCTCAAATTGAGATCATAGGCTTTTTGAAGATTG
CTCAAATTATG
CTTCTCATATTGCATGAGCATTTTGAAGCCCGCGTCATCAACCAAAGCATTTTTTCCACCCATCA
CAATGATTTTAT CATTTTCTTTAAAATT

FIGURE 6B

```
MKVNVSCSSV QTTIDILEEN QGEDESILTL GQLRDRIATD NDVDVETMKL    50
LHRGKFLQGA DDVSLSTLNF KENDKIIVMG GKNALVDDAG FKMLMQYEKH   100
NLSNLQKAYD LNLRDVADLE RGFLEKPKQV EMGKKLEKKV KYFNEEAERH   150
LETLDGMNII TETTPENQAK RNREKRKTLV NGIQTLLNQN DALLRRLQEY   200
QSVLNGDIPE                                              210
```

FIGURE 7A

```
ATGCCAGTCG TGAACATACC AATCAAAATA CTTGGTCAGA ATCAATCACA     50
TAGTCGAAGT AACTCCTCGT CTTCTGTTGA CAACGATCGA AATCAACCAC    100
CACAGCAGCC ACCTCAACCG CAACCACAAC AGCAATCTCA GCAACAATAC    150
CAGCAGGCTC CAAACGTGAA TACCAATATG CATCATTCCA ACGGATTCTC    200
ACCTAACTTC CCATCTCGTA GTCCTATTCC GGACTTTCCC AGTTTTTCAT    250
CTGGGTTCCC AAACGATTCT GAATGGTCTT CGAATTTCCC GTCGTTTCCA    300
AATTTCCCAA GTGGATTCTC AAATGGAAGT TCTAATTTCC CTGATTTTCC    350
AAGATTCGGA AGAGATGGAG GACTATCGCC AAACCCACCG ATGCAAGGAT    400
ACAGGAGAAG TCCAACACCA ACATCAACTC AATCTCCAAC TTCTACATTA    450
AGACGCAACT CTCAGCAGAA TCAAGCTCCT CCACAATATT CTCAGCAACA    500
ACCACAACAA GCTCAACAAC GTCAGACAAC TCCTCCGTCA ACAAAAGCTT    550
CATCTCGACC ACCATCTCGT ACTCGTGAAC CAAAGGAACC TGAGGTACCC    600
GAGAGACCAG CAGTTATTCC ATTGCCATAT GAGAAGAAGG AGAAACCACT    650
GGAGAAGAAA GGTAGTCGTG ATTCTGGAAA GGGTGATGAG AACCTTGAAG    700
AGAACATTGC CAAGATCACG ATCGGAAAGA ATAATTGCGA GTTATGTCCG    750
GAACAAGAAA CGGACGGCGA CCCATCTCCA CTAACCTCCC CAATCACCGA    800
AGGAAAGCCA AAGAGAGGAA AGAAACTTCA ACGTAATCAA AGTGTTGTTG    850
ATTTCAATGC CAAGACAATT GTTACTTTGG ATAAAATTGA ATTACAAGTT    900
GAGCAGTTGA GAAAAAAAGC TGCTGAACTC GAAATGGAAA AAGAGCAAAT    950
TCTTCGTTCT CTAGGAGAAA TCAGTGTTCA TAACTGCATG TTCAAACTGG   1000
AAGAATGTGA TCGTGAAGAG ATTGAAGCAA TCACTGACCG ATTGACAAAA   1050
AGAACAAAGA CAGTTCAAGT TGTTGTCGAA ACTCCACGAA ATGAAGAACA   1100
GAAAAAAGCA CTGGAAGATG CAACTTTGAT GATCGATGAA GTCGGAGAAA   1150
TGATGCATTC GAATATTGAA AAGGCTAAGC TGTGCCTACA AACCTACATG   1200
AACGCCTGTT CGTACGAAGA AACTGCTGGA GCCACCTGCC AAAACTTCTT   1250
GAAGATCATA ATTCAGTGCG CTGCTGATGA TCAGAAACGC ATCAAGCGTC   1300
GTCTGGAAAA TCTGATGTCT CAAATTGAGA ATGCTGAGAG AACGAAAGCA   1350
GATTTGATGG ATGATCAAAG CGAATAG                            1377
```

FIGURE 7B

```
MPVVNIPIKI LGQNQSHSRS NSSSSVDNDR NQPPQQPPQP QPQQQSQQQY      50
QQAPNVNTNM HHSNGFSPNF PSRSPIPDFP SFSSGFPNDS EWSSNFPSFP     100
NFPSGFSNGS SNFPDFPRFG RDGGLSPNPP MQGYRRSPTP TSTQSPTSTL     150
RRNSQQNQAP PQYSQQQPQQ AQQRQTTPPS TKASSRPPSR TREPKEPEVP     200
ERPAVIPLPY EKKEKPLEKK GSRDSGKGDE NLEENIAKIT IGKNNCELCP     250
EQETDGDPSP LTSPITEGKP KRGKKLQRNQ SVVDFNAKTI VTLDKIELQV     300
EQLRKKAAEL EMEKEQILRS LGEISVHNCM FKLEECDREE IEAITDRLTK     350
RTKTVQVVVE TPRNEEQKKA LEDATLMIDE VGEMMHSNIE KAKLCLQTYM     400
NACSYEETAG ATCQNFLKII IQCAADDQKR IKRRLENLMS QIENAERTKA     450
DLMDDQSE                                                   458
```

FIGURE 8A

```
ATGTCAGAAA AGACTAGCAC AGTTACAATA CACTATGGAA ATCAGCGATT     50
TCCGGTAGCA GTCAATCTAA ATGAGACGTT AAGTGAACTG ATTGATGATT    100
TACTTGAAAC GACTGAGATT TCTGAGAAGA AAGTCAAGCT TTTTTACGCT    150
GGCAAGCGTT TAAAAGACAA AAAAGCCTCG TTATCAAAAT TGGGTTTAAA    200
AAATCATAGT AAAATTCTAT GTATAAGACC ACATAAGCAA CAACGAGGTT    250
CCAAGGAAAA AGACACGGTT GAGCCCGCTC CGAAAGCGGA AGCGGAGAAT    300
CCTGTATTTT CGCGTATTTC TGGAGAAATA AAAGCCATCG ATCAGTATGT    350
TGACAAAGAA CTTTCCCCCA TGTACGACAA TTACGTAAAT AAACCGTCGA    400
ACGATCCAAA GCAGAAAAAC AAACAGAAAC TAATGATAAG TGAACTACTT    450
TTACAACAGC TTTTAAAATT GGATGGAGTT GACGTACTGG GCAGCGAGAA    500
ATTGCGTTTT GAACGGAAGC AACTTGTTTC TAAGATCCAA AAAATGTTGG    550
ATCACGTTGA CCAAACAAGC CAAGAAGTGG CCGCATAG                 588
```

FIGURE 8B

```
MSEKTSTVTI HYGNQRFPVA VNLNETLSEL IDDLLETTEI SEKKVKLFYA    50
GKRLKDKKAS LSKLGLKNHS KILCIRPHKQ QRGSKEKDTV EPAPKAEAEN   100
PVFSRISGEI KAIDQYVDKE LSPMYDNYVN KPSNDPKQKN KQKLMISELL   150
LQQLLKLDGV DVLGSEKLRF ERKQLVSKIQ KMLDHVDQTS QEVAA        195
```

FIGURE 9A

```
ATGTCTTTTT TTACCCAGTT GTGTTCTATG GATAAAAAAT ATTGGATCTC     50
TCTAGCTGTA TTGTCAGTTA CTGTTTTGAT TAGCGCATTA TTGAAAAAGA    100
GAGCTACTGA AACCGAAGAT ATTGTCGTTG TTCATTACGA TGGCGAAAAG    150
TTGAATTTTG TGTTGCGACA ACCAAGGCTG AATATGGTTT CTTACACTAG    200
TTTTCTTCGT CGCGTGTGCA ACGCATTTTC AGTAATGCCC GACAAAGCGT    250
CTCTCAAGTT AAACGGGGTG ACCCTCAAGG ATGGTTCACT TTCCGACCAA    300
AATGTGCAAA ATGGAAGTGA ATTAGAGCTC GAATTACCCA AACTGAGCCC    350
GGCAATGCAA CAAATTGAAG CATATATAGA TGAGCTTCAA CAGGATCTCG    400
TCCCTAAAAT TGAAGCCTTC TGCCAATCGT CTCCCGCTTC GGCACAAGAT    450
GTTCAAGATT TGCATACACG CCTTAGTGAA ACATTGTTGG CTAGGATGAT    500
AAAATTAGAT GCTGTTAATG TTGAAGACGA CCCAGAAGCT CGTCTTAAAA    550
GAAAAGAAGC TATTCGTTTA TCTCAACAAT ATTTGAGTAA ACTAGATTCC    600
ACCAAGAATC AAAACAAATG A                                   621
```

FIGURE 9B

MSFFTQLCSM	DKKYWISLAV	LSVTVLISAL	LKKRATETED	IVVVHYDGEK	50
LNFVLRQPRL	NMVSYTSFLR	RVCNAFSVMP	DKASLKLNGV	TLKDGSLSDQ	100
NVQNGSELEL	ELPKLSPAMQ	QIEAYIDELQ	QDLVPKIEAF	CQSSPASAQD	150
VQDLHTRLSE	TLLARMIKLD	AVNVEDDPEA	RLKRKEAIRL	SQQYLSKLDS	200
TKNQNK					206

FIGURE 10A

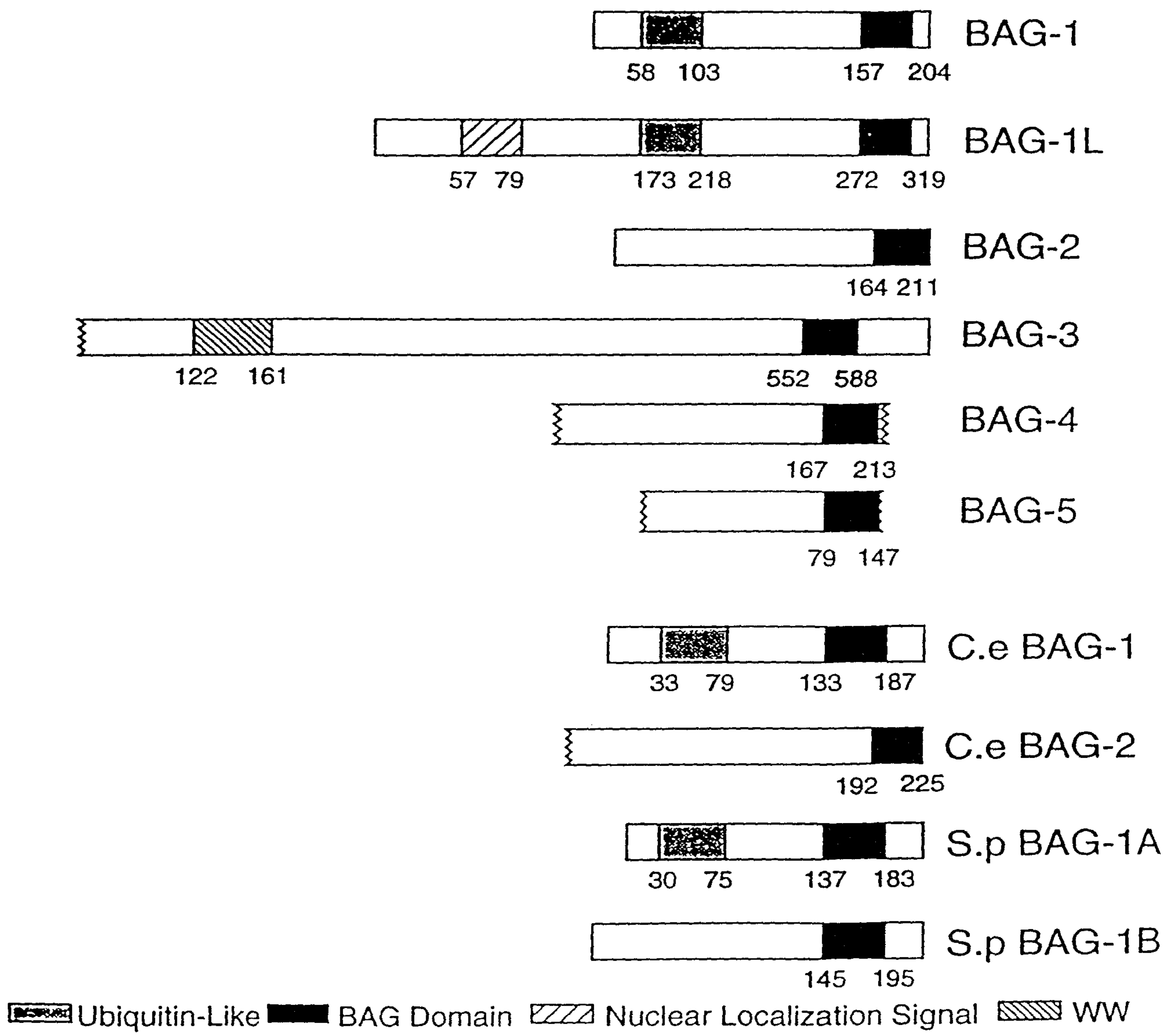
BAG-1
58 103 157 204
BAG-1L
57 79 173 218 272 319
BAG-2
164 211
BAG-3
122 161 552 588
BAG-4
167 213
BAG-5
79 147
C.e BAG-1
33 79 133 187
C.e BAG-2
192 225
S.p BAG-1A
30 75 137 183
S.p BAG-1B
145 195
Ubiquitin-Like
BAG Domain
Nuclear Localization Signal
WW

FIGURE 10B

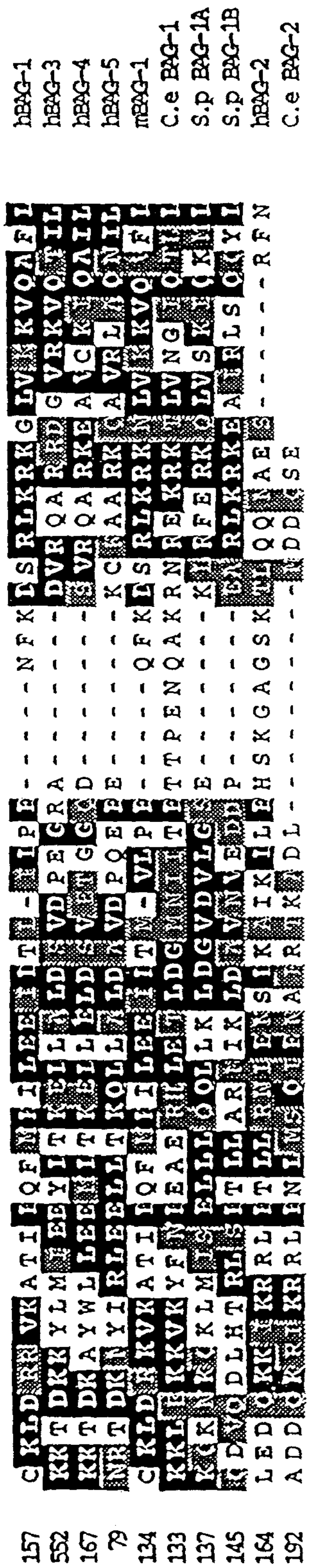

FIGURE 11

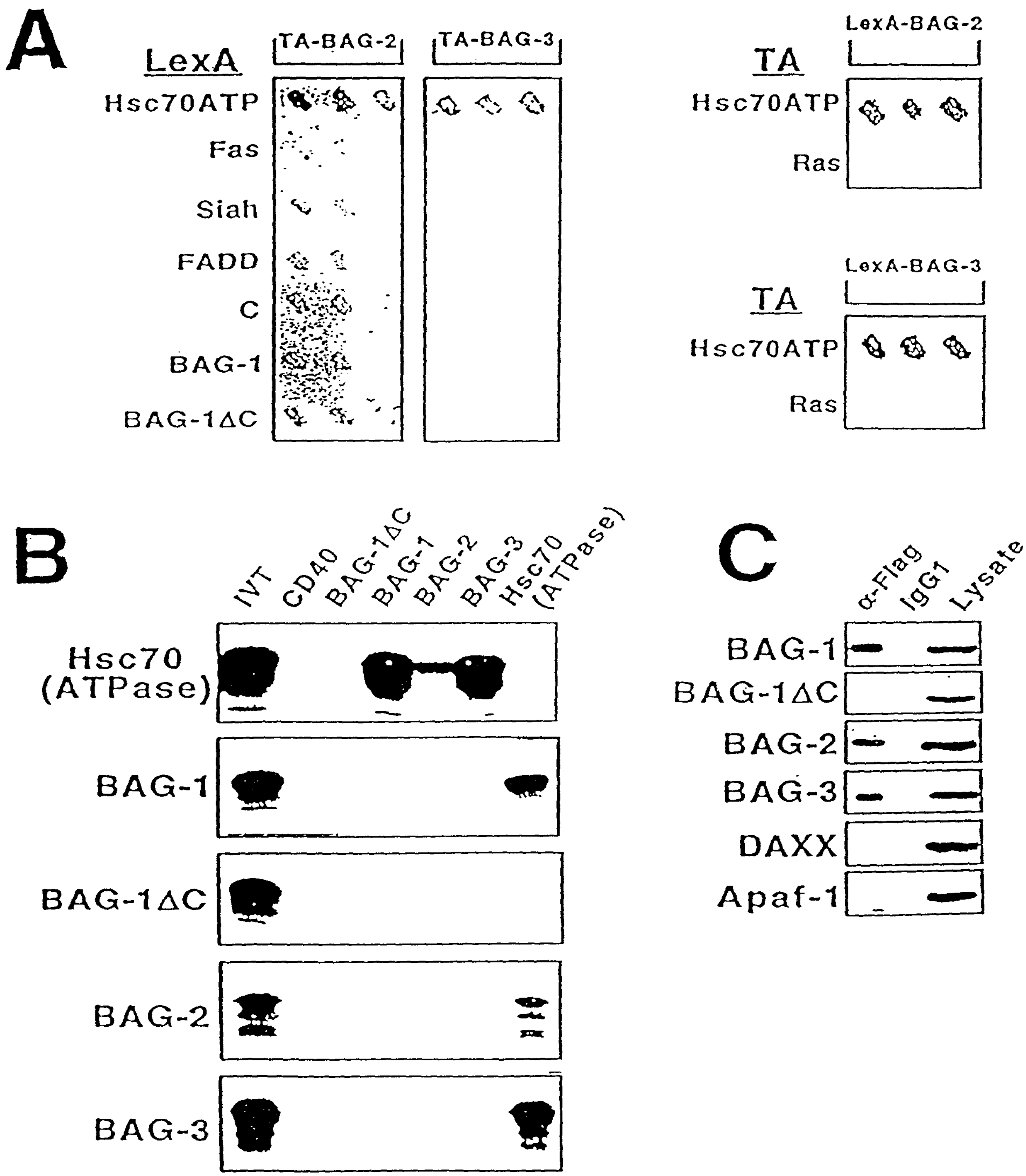
A
LexA
TA-BAG-2
TA-BAG-3
Hsc70ATP
Fas
Siah
FADD
C
BAG-1
BAG-1ΔC
TA
LexA-BAG-2
Hsc70ATP
Ras
TA
LexA-BAG-3
Hsc70ATP
Ras
B
IVT
CD40
BAG-1ΔC
BAG-1
BAG-2
BAG-3
Hsc70 (ATPase)
Hsc70 (ATPase)
BAG-1
BAG-1ΔC
BAG-2
BAG-3
C
α-Flag
IgG1
Lysate
BAG-1
BAG-1ΔC
BAG-2
BAG-3
DAXX
Apaf-1

FIGURE 12

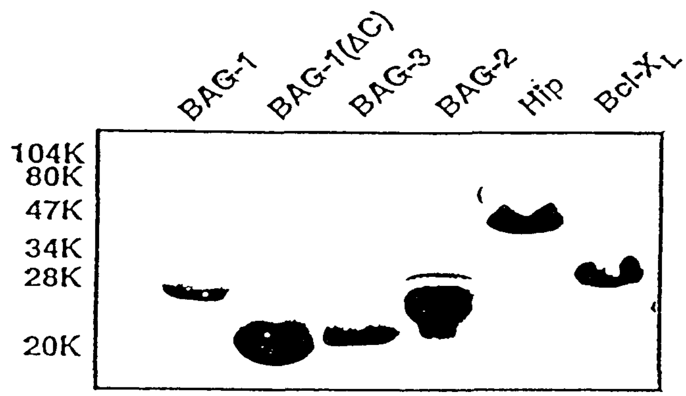

FIGURE 13

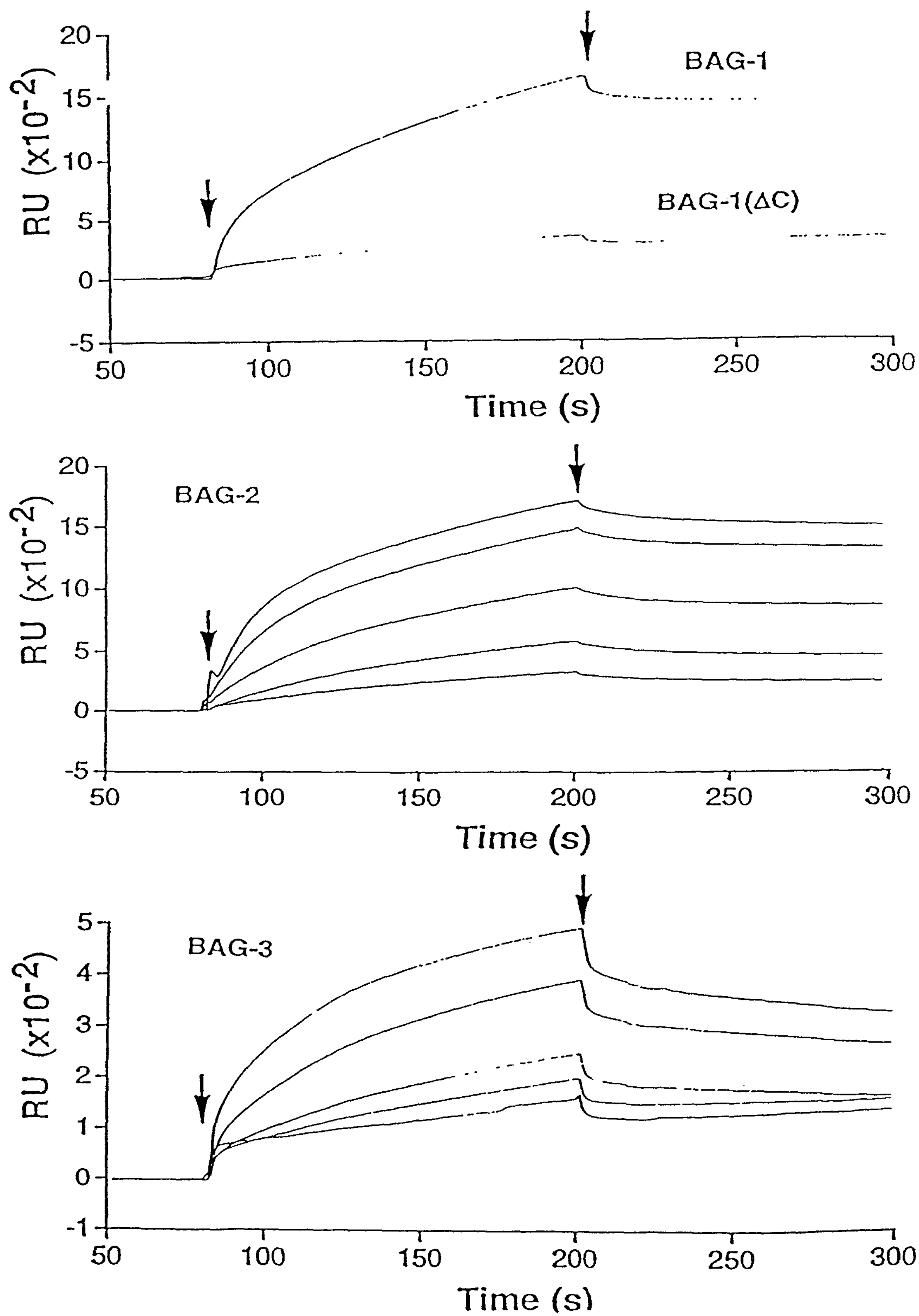
BAG-1
BAG-1(ΔC)
RU (x10-2)
Time (s)
BAG-2
RU (x10-2)
Time (s)
BAG-3
RU (x10-2)
Time (s)

FIGURE 14

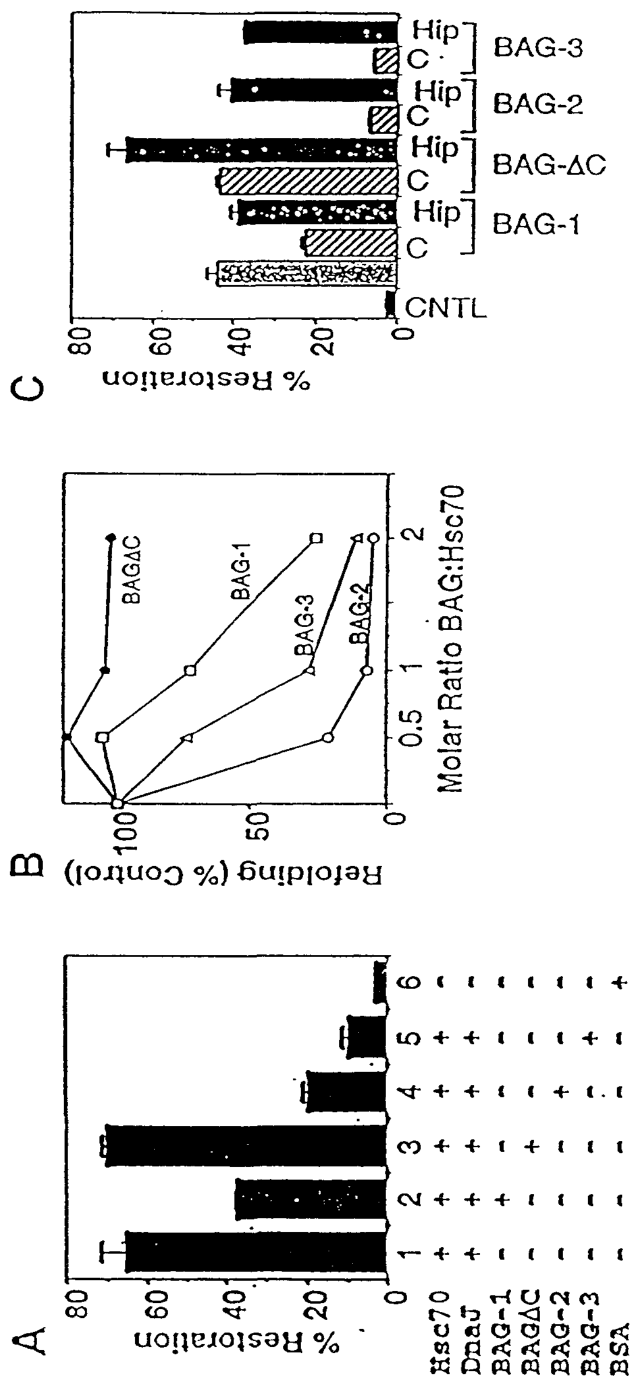
A
% Restoration
80
60
40
20
0
1
2
3
4
5
6
Hsc70
DnaJ
BAG-1
BAGΔC
BAG-2
BAG-3
BSA
B
Refolding (% Control)
100
50
0
0.5
1
2
Molar Ratio BAG:Hsc70
BAGΔC
BAG-1
BAG-3
BAG-2
C
% Restoration
80
60
40
20
0
CNTL
C
Hip
BAG-1
BAG-ΔC
BAG-2
BAG-3

FIGURE 15A

```
GCGGAGCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGGACTGGA     50
CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC TCCTCCTTCC    100
CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC    150
ACGTCACCCC CGCCTTTAAT TCATAAAGGT GCCCGGCGCC GGCTTCCCGG    200
ACACGTCGGC GGCGGAGAGG GGCCCACGGC GGCGGCCCGG CCAGAGACTC    250
GGCGCCCGGA GCCAGCGCCC CGCACCCGCG CCCCAGCGGG CAGACCCCAA    300
CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG    350
CAACGGTGAC CGCGACCCTT TGCCCCCCGG ATGGGAGATC AAGATCGACC    400
CGCAGACCGG CTGGCCCTTC TTCGTGGACC ACAACAGCCG CACCACTACG    450
TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC    500
TGCCAATGGC CCTTCCCGGG AGGGCTCTAG GCTGCCGCCT GCTAGGGAAG    550
GCCACCCTGT GTACCCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG    600
CTCCATGAAG GCGCTGAGAA CCGGCAGGTG CACCCTTTCC ATGTCTATCC    650
CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC    700
AGAGGTCCCA GTCACCTCTG CGGGGCATGC CAGAAACCAC TCAGCCAGAT    750
AAACAGTGTG GACAGGTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC    800
CCACGGACCT GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT    850
CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT    900
CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA    950
CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC CAGAAGACGC   1000
ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC   1050
AAGATCCAGG GGGATGACTG GGAGCCCCGG CCCCTGCGGG CGGCATCCCC   1100
GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGGGC TCACCAGCCA   1150
GGAGCAGCAC GCCACTCCAC TCCCCCTCGC CCATCCGTGT GCACACCGTG   1200
GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC   1250
CCAGCCTGAA AACAAACCAG AAAGTAAGCC AGGCCCAGTT GGACCAGAAC   1300
TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT   1350
```

FIGURE 15A

```
AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTGAGAAGG TAGAGGTGAA   1400
AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT GGCCCTTCTG   1450
CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC   1500
AGCACTGCCC CTGCAGAAGC TACACCTCCA AAACCAGGAG AAGCCGAGGC   1550
TCCCCCAAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAGG   1600
TGCAGGGGCT GGAGCAGGCT GTAGACAACT TTGAAGGCAA GAAGACTGAC   1650
AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT   1700
GGATTCAGTG GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG   1750
ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC   1800
ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT   1850
TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT GCCGTGGCAG   1900
CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA   1950
ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG ACTTCAAACC CCAGCAGCAT   2000
GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA   2050
ATCAGACTCG GAACCGATGT GTGCTTTAGG GAATTTTAAG TTGCATGCAT   2100
TTCAGAGACT TTAAGTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA   2150
ACTTGGGTGG AGGCAAAACA CTAATAAAAG GGCTAAAAAG GAAAATGATG   2200
CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAAGAAGTT GCTTGTTGTT   2250
TGAGAAGTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC   2300
CCCCACCACC TGTTAGCTGT GGTTGTGCAC TGTCTTTTGT AGCTCTGGAC   2350
TGGAGGGGTA GATGGGGAGT CAATTACCCA TCACATAAAT ATGAAACATT   2400
TATCAGAAAT GTTGCCATTT TAATGAGATG ATTTTCTTCA TCTCATAATT   2450
AAAATACCTG ACTTTAGAGA GAGTAAAATG TGCCAGGAGC CATAGGAATA   2500
TCTGTATGTT GGATGACTTT AATGCTACAT TTTC                    2534
```

FIGURE 15B

MSAATHSPMM QVASGNGDRD PLPPGWEIKI DPQTGWPFFV DHNSRTTTWN 50
DPRVPSEGPK ETPSSANGPS REGSRLPPAR EGHPVYPQLR PGYIPIPVLH 100
EGAENRQVHP FHVYPQPGMQ RFRTEAAAAA PQRSQSPLRG MPETTQPDKQ 150
CGQVAAAAAA QPPASHGPER SQSPAASDCS SSSSSASLPS SGRSSLGSHQ 200
LPRGYISIPV IHEQNVTRPA AQPSFHKAQK THYPAQRGEY QTHQPVYHKI 250
QGDDWEPRPL RAASPFRSSV QGASSREGSP ARSSTPLHSP SPIRVHTVVD 300
RPQQPMTHRE TAPVSQPENK PESKPGPVGP ELPPGHIPIQ VIRKEVDSKP 350
VSQKPPPPSE KVEVKVPPAP VPCPPPSPGP SAVPSSPKSV ATEERAAPST 400
APAEATPPKP GEAEAPPKHP GVLKVEAILE KVQGLEQAVD NFEGKKTDKK 450
YLMIEEYLTK ELLALDSVDP EGRADVRQAR RDGVRKVQTI LEKLEQKAID 500
VPGQVQVYEL QPSNLEADQP LQAIMEMGAV AADKGKKNAG NAEDPHTETQ 550
QPEATAAATS NPSSMTDTPG NPAAP 575

FIGURE 15C

```
CGGGACCTCC GCATCCAACC CCGGGCCGCG GCCAACTTCT CTGCACTGGA CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC     90
TCCTCCTTCC CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC ACGTCACCCC CGCCTTTAAT TCATAAAGGT    180
GCCCGGCGCC GGCTTCCCGG ACACCTCGGC GGCGGAGAGG GGCCCACGCC GGCGGCCCGG CCAGACACTC GGCGGCCCGA GCCAGCGCCC    270
CGCACCCGCG CCCCAGCGGG CAGACCCCAA CCCAGCATGA GCGCCGCCAC CCACTCGCCC ATGATGCAGG TGGCGTCCGG CAACGGTGAC    360
                                     M S  A A T  H S P  M M Q V  A S G  N G D

CGCGACCCTT TGCCCCCCGG ATGGCAGATC AACATCCACC CCCAGACCCC CTGGCCCTTC TTCGTCCACC ACAACAGCCG CACCACTACG    450
R D P L  P P G  W I I  H I D P  Q T G  W P I  I V D H  N S R  T T T

TGGAACGACC CGCGCGTGCC CTCTGAGGGC CCCAAGGAGA CTCCATCCTC TGCCAATGGC CCTTCCCGCG AGGGCTCTAG GCTGCCGCCT    540
W N D P  R V P  S I G  P K E T  P S S  A N G  P S R I  G S R  L P P

GCTAGCGAAG GCCACCCTGT GTACCCCCAG CTCCGACCAG GCTACATTCC CATTCCTGTG CTCCATGAAG GCGCTGAGAA CCGGCAGGTG    630
A R I G  H P V  Y P Q  L R P G  Y I P  I P V  L H I G  A I N  R Q V

CACCCTTTCC ATGTCTATCC CCAGCCTGGG ATGCAGCGAT TCCGAACTGA GGCGGCAGCA GCGGCTCCTC AGAGGTCCCA GTCACCTCTG    720
H P I H  V Y P  Q P G  M Q R I  R T I  A A A  A A P Q  R S Q  S P L

CGGGCCATGC CAGAAACCAC TCAGCCAGAT AAACAGTGTG GACAGCTGGC AGCGGCGGCG GCAGCCCAGC CCCCAGCCTC CCACGGACCT    810
R G M P  I T T  Q P D  K Q C G  Q V A  A A A  A A Q P  P A S  H G P

GAGCGGTCCC AGTCTCCAGC TGCCTCTGAC TGCTCATCCT CATCCTCCTC GGCCAGCCTG CCTTCCTCCG GCAGGAGCAG CCTGGGCAGT    900
I R S Q  S P A  A S D  C S S S  S S S  A S L  P S S G  R S S  L G S

CACCAGCTCC CGCGGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA CGTTACCCGG CCAGCAGCCC AGCCCTCCTT CCACAAAGCC    990
H Q L P  R G Y  I S I  P V I H  I Q N  V T R  P A A Q  P S I  H K A

CAGAAGACCC ACTACCCAGC GCAGAGGGGT GAGTACCAGA CCCACCAGCC TGTGTACCAC AAGATCCAGG GGGATGACTG GGAGCCCCGG   1080
Q K T H  Y P A  Q R G  I Y Q T  H Q P  V Y H  K I Q G  D D W  I P R

CCCCTGCGGG CGGCATCCCC GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGGAGCGC TCACCAGCCA GCAGCACCAC GCCACTCCAC   1170
P L R A  A S P  I R S  S V Q G  A S S  R I G  S P A R  S S T  P L H

TCCCCCTCGC CCATCCGTGT GCACACCGTG GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAAACTG CACCTGTTTC CCAGCCTGAA   1260
S P S P  I R V  H T V  V D R P  Q Q P  M T H  R I T A  P V S  Q P I

AACAAACCAG AAAGTAAGCC AGCCCCAGTT GGACCAGAAC TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAAGA GGTGGATTCT   1350
N K P I  S K P  G P V  G P I L  P P G  H I P  I Q V I  R K I  V D S

AAACCTGTTT CCCAGAAGCC CCCACCTCCC TCTCAGAAGG TAGAGGTGAA AGTTCCCCCT GCTCCAGTTC CTTGTCCTCC TCCCAGCCCT   1440
K P V S  Q K P  P P P  S I K V  I V K  V P P  A P V P  C P P  P S P

GGCCCTTCTG CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GCCAGCCCCC AGCACTGCCC CTGCAGAAGC TACACCTCCA   1530
G P S A  V P S  S P K  S V A T  I I R  A A P  S T A P  A I A  T P P

AAACCAGGAG AAGCCGAGCC TCCCCCAAAA CATCCAGGAG TGCTCAAAGT GGAAGCCATC CTGGAGAAGG TGCAGGGGCT GGAGCAGGCT   1620
K P G I  A I A  P P K  H P G V  L K V  I A I  L I K V  Q G L  I Q A

GTAGACAACT TTGAAGGCAA GAAGACTGAC AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT GGATTCAGTG   1710
V D N Y  I G K  K T D  K K Y L  M I I  I Y L  T K I L  L A L  D S V

GACCCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG ACGGTGTCAG GAAGGTTCAG ACCATCTTGG AAAAACTTGA ACAGAAAGCC   1800
D P I G  R A D  V R Q  A R R D  G V R  K V Q  T I L I  K L I  Q K A

ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT   1890
I D V P  G Q V  Q V Y  I L Q P  S N L  I A D  Q P L Q  A I M  I M G

GCCGTGGCAG CAGACAAGGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA ACCCAGCAGC CAGAAGCCAC AGCAGCAGCG   1980
A V A A  D K G  K K N  A G N A  I D P  H T I  T Q Q P  I A T  A A A

ACTTCAAACC CCAGCAGCAT GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA ATCAGACTCG GAACCGATGT   2070
T S N P  S S M  T D T  P G N P  A A P  .

CTGCTTTTGG GAATTTTAAC TTGCATGCAT TTCAGACACT TTAACTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA ACTTGCCTGG   2160
AGGCAAAACA CTAATAAAAC GGCTAAAAAC GAAAATGATG CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAACAACTT GCTTGTTGTT   2250
TGAGAACTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC CCCCACCCACC TGTTAGCTGT GGTTGTCCAC TGTCTTTTGT   2340
AGCTCTGCAC TGCAGCGGTA GATGGCAGT CAATTAGCCA TCAGTAAAT ATGAAACATT TATCAGAAAT GTTGCCATTT TAATGACATG   2430
ATTTTCTTCA TCTCATAATT AAAATACCTG ACTTTACACA GAGTAAAATG TCCCAGCACC CATACCAATA TCTGTATGTT GGATGACTTT   2520
AATGCTACAT TTTC                                                                                       2534
```

FIGURE 16A

```
CGGTGGGAGC GGGGCGGGAA GCGCTTCAGG GCAGCGGATC CCATGTCGGC     50
CCTGAGGCGC TCGGGCTACG GCCCCAGTGA CGGTCCGTCC TACGGCCGCT    100
ACTACGGGCC TGGGGGTGGA GATGTGCCGG TACACCCACC TCCACCCTTA    150
TATCCTCTTC GCCCTGAACC TCCCCAGCCT CCCATTTCCT GGCGGGTGCG    200
CGGGGGCGGC CCGGCGGAGA CCACCTGGCT GGGAGAAGGC GGAGGAGGCG    250
ATGGCTACTA TCCCTCGGGA GGCGCCTGGC CAGAGCCTGG TCGAGCCGGA    300
GGAAGCCACC AGGAGCAGCC ACCATATCCT AGCTACAATT CTAACTATTG    350
GAATTCTACT GCGAGATCTA GGGCTCCTTA CCCAAGTACA TATCCTGTAA    400
GACCAGAATT GCAAGGCCAG AGTTTGAATT CTTATACAAA TGGAGCGTAT    450
GGTCCAACAT ACCCCCCAGG CCCTGGGGCA AATACTGCCT CATACTCAGG    500
GGCTTATTAT GCACCTGGTT ATACTCAGAC CAGTTACTCC ACAGAAGTTC    550
CAAGTACTTA CCGTTCATCT GGCAACAGCC CAACTCCAGT CTCTCGTTGG    600
ATCTATCCCC AGCAGGACTG TCAGACTGAA GCACCCCCTC TTAGGGGGCA    650
GGTTCCAGGA TATCCGCCTT CACAGAACCC TGGAATGACC CTGCCCCATT    700
ATCCTTATGG AGATGGTAAT CGTAGTGTTC CACAATCAGG ACCGACTGTA    750
CGACCACAAG AAGATGCGTG GGCTTCTCCT GGTGCTTATG GAATGGGTGG    800
CCGTTATCCC TGGCCTTCAT CAGCGCCCTC AGCACCACCC GGCAATCTCT    850
ACATGACTGA AAGTACTTCA CCATGGCCTA GCAGTGGCTC TCCCCAGTCA    900
CCCCCTTCAC CCCCAGTCCA GCAGCCCAAG GATTCTTCAT ACCCCTATAG    950
CCAATCAGAT CAAAGCATGA ACCGGCACAA CTTTCCTTGC AGTGTCCATC   1000
AGTACGAATC CTCGGGGACA GTGATCAATG AAGATTCAGA TCTTTTGGAT   1050
TCCCAAGTCC AGTATAGTGC TGAGCCTCAG CTGTATGGTA ATGCCACCAG   1100
TGACCATCCC AACAATCAAG ATCAAAGTAG CAGTCTTCCT GAAGAATGTG   1150
TACCTTCAGA TGAAAGTACT CCTCCGAGTA TTAAAAAAAT CATACATGTG   1200
CTGGAGAAGG TCCAGTATCT TGAACAAGAA GTAGAAGAAT TTGTAGGAAA   1250
AAAGACAGAC AAAGCATACT GGCTTCTGGA AGAAATGCTA ACCAAGGAAC   1300
```

FIGURE 16A

```
TTTTGGAACT GGATTCAGTT GAAACTGGGG GCCAGGACTC TGTACGGCAG   1350
GCCAGAAAAG AGGCTGTTTG TAAGATTCAG GCCATACTGG AAAAATTAGA   1400
AAAAAAAGGA TTATGAAAGG ATTTAGAACA AAGTGGAAGC CTGTTACTAA   1450
CTTGACCAAA GAACACTTGA TTAGGTTAAT TACCCTCTTT TTGAAATGCC   1500
TGTTGATGAC AAGAAGCAAT ACATTCCAGC TTTTCCTTTG ATTTTATACT   1550
TGAAAAACTG GCAAAGGAAT GGAAGAATAT TTTAGTCATG AAGTTGTTTT   1600
CAGTTTTCAGA CGAATGAATG TAATAGGAAA CTATGGAGTT ACCAATATTG  1650
CCAAGTAGAC TCACTCCTTA AAAAATTTAT GGATATCTAC AAGCTGCTTA   1700
TTACCAGCAG GAGGGAAACA CACTTCACAC AACAGGCTTA TCAGAAACCT   1750
ACCAGATGAA ACTGGATATA ATTTGAGACA AACAGGATGT GTTTTTTTAA   1800
ACATCTGGAT ATCTTGTCAC ATTTTTGTAC ATTGTGACTG CTTTCAACAT   1850
ATACTTCATG TGTAATTATA GCTTAGACTT TAGCCTTCTT GGACTTCTGT   1900
TTTGTTTTGT TATTTGCAGT TTACAAATAT AGTATTATTC TCTAAAAAA    1950
AAAAAAAAAA AAAAAA                                         1966
```

FIGURE 16B

MSALRRSGYGPSDGPSYGRYYGPGGGDVPVHPPPPLYPLRPEPPQPPISWRVRGGGPAETTWLGEGGGGDGYYPSGGAWP
EPGRAGGSHQEQPPYPSYNSNYWNSTARSRAPYPSTYPVRPELQGQSLNSYTNGAYGPTYPPGPGANTASYSGAYYAPGY
TQTSYSTEVPSTYRSSGNSPTPVSRWIYPQQDCQTEAPPLRGQVPGYPPSQNPGMTLPHYPYGDGNRSVPQSGPTVRPQE
DAWASPGAYGMGGRYPWPSSAPSAPPGNLYMTESTSPWPSSGSPQSPPSPPVQQPKDSSYPYSQSDQSMNRHNFPCSVHQ
YESSGTVINEDSDLLDSQVQYSAEPQLYGNATSDHPNNQDQSSSLPEECVPSDESTPPSIKKIIHVLEKVQYLEQEVEEF
VGKKTDKAYWLLEEMLTKELLELDSVETGGQDSVRQARKEAVCKIQAILEKLEKKGL

FIGURE 16C

```
CGCTGGCAGCGGGGCGGGAAGCGCTTCACCCCAGCGGATCCCATGTCGGCCCTGAAGCGCTCGGGCTACGGCCCCAGTGACGGTCCCTCC    90
                                          M  S  A  L  K  R  S  G  Y  G  P  S  D  G  P  S

TACGGCCGCTACTACGGGCCTGGGGGTGGAGATGTGCCGGTACACCCACCTCCACCCTTATATCCTCTTCGCCCTGAACCTCCCCAGCCT    180
Y  G  R  Y  Y  G  P  G  G  G  D  V  P  V  H  P  P  P  P  L  Y  P  L  R  P  E  P  P  Q  P

CCCATTTCCTGGCGGGTGCGCGGGGGCGGCCCGGCCCACACCACCTGGCTGGGAGAAGGCGGAGGAGGCGATGGCTACTATCCCTCGGGA    270
P  I  S  W  R  V  R  G  G  G  P  A  H  T  T  W  L  G  E  G  G  G  G  D  G  Y  Y  P  S  G

GGCGCCTGGCCAGAGCCTGGTCGAGCCGGAGGAAGCCACCAGGAGCAGCCACCATATCCTAGCTACAATTCTAACTATTGGAATTCTACT    360
G  A  W  P  E  P  G  R  A  G  G  S  H  Q  E  Q  P  P  Y  P  S  Y  N  S  N  Y  W  N  S  T

CCCAGATCTAGGGCTCCTTACCCAAGTACATATCCTGTAAGACCAGAATTGCAAGGCCAGAGTTTGAATTCTTATACAAATGGAGCGTAT    450
P  R  S  R  A  P  Y  P  S  T  Y  P  V  R  P  E  L  Q  G  Q  S  L  N  S  Y  T  N  G  A  Y

GGTCCAACATACCCCCCACCCCCTGGGGCAAATACTGCCTCATACTCAGCGGCTTATTATGCACCTGGTTATACTCAGACCAGTTACTCC    540
G  P  T  Y  P  P  P  P  G  A  N  T  A  S  Y  S  A  A  Y  Y  A  P  G  Y  T  Q  T  S  Y  S

ACAGAAGTTCCAACTACTTACCGTTCATCTGGCAACAGCCCAACTCCAGTCTCTCGTTGGATCTATCCCCAGCAGGACTGTCAGACTGAA    630
T  E  V  P  T  T  Y  R  S  S  G  N  S  P  T  P  V  S  R  W  I  Y  P  Q  Q  D  C  Q  T  E

GCACCCCCTCTTAGGTGCCAGGTTCCAGGATATCCGCCTTCACAGAACCCTGGAATGACCCTGCCCCATTATCCTTATGGAGATGGTAAT    720
A  P  P  L  R  C  Q  V  P  G  Y  P  P  S  Q  N  P  G  M  T  L  P  H  Y  P  Y  G  D  G  N

CGTAGTGTTCCACAATCAGGACCGACTGTACGACCACAAGAAGATGCGTGGGCTTCTCCTGGTGCTTATGGAATGGGTGGCCGTTATCCC    810
R  S  V  P  Q  S  G  P  T  V  R  P  Q  E  D  A  W  A  S  P  G  A  Y  G  M  G  G  R  Y  P

TGGCCTTCATCAGCGCCCTCAGCACCACCCGGCAATCTCTACATGACTGAAAGTACTTCACCATGGCCTAGCAGTGGCTCTCCCCAGTCA    900
W  P  S  S  A  P  S  A  P  P  G  N  L  Y  M  T  E  S  T  S  P  W  P  S  S  G  S  P  Q  S

CCCCCTTCACCCCCAGTCCAGCAGCCCAAGGATTCTTCATACCCCTATAGCCAATCAGATCAAAGCATGAACCGGCACAACTTTCCTTGC    990
P  P  S  P  P  V  Q  Q  P  K  D  S  S  Y  P  Y  S  Q  S  D  Q  S  M  N  R  H  N  F  P  C

AGTTTCCATCAGTACGAATCCTCCGGGACAGTGAACAATGAAGATTCAGATCTTTTGGATTCCCAAGTCCAGTATAGTGCTGAGCCTCAG    1080
S  F  H  Q  Y  E  S  S  G  T  V  N  N  E  D  S  D  L  L  D  S  Q  V  Q  Y  S  A  E  P  Q

CTGTATGGTAATGCCACCAGTGACCATCCCAACAATCAAGATCAAAGTAGCAGTCTTCCTGAAGAATGTGTACCTTCAGATGAAAGTACT    1170
L  Y  G  N  A  T  S  D  H  P  N  N  Q  D  Q  S  S  S  L  P  E  E  C  V  P  S  D  E  S  T

CCTCCGAGTATTAAAAAAATCATACATGTGCTGGAGAAGGTCCAGTATCTTGAACAAGAAGTAGAAGAATTTGTAGGAAAAAAGACAGAC    1260
P  P  S  I  K  K  I  I  H  V  L  E  K  V  Q  Y  L  E  Q  E  V  E  E  F  V  G  K  K  T  D

AAAGCATACTGGCTTCTGGAAGAAATGCTAACCAAGGAACTTTTGGAACTGGATTCAGTTGAAACTGGGGGCCAGGACTCTGTACGGCAG    1350
K  A  Y  W  L  L  E  E  M  L  T  K  E  L  L  E  L  D  S  V  E  T  G  G  Q  D  S  V  R  Q

GCCAGAAAAGAGGCTGTTTGTAAGATTCAGGCCATACTGGAAAAATTAGAAAAAAAAGGATTATGAAAGGATTTAGAACAAAGTGGAAGC    1440
A  R  K  E  A  V  C  K  I  Q  A  I  L  E  K  L  E  K  K  G  L  .

CTGTTACTAACTTGACCAAAGAACACTTCATTAGGTTAATTACCCTCTTTTTGAAATGCCTGTTGATGACAACAACCAATACATTCCAGC    1530
TTTTCCTTTGATTTTATACTTGAAAAACTGGCAAAGGAATGGAAGAATATTTTAGTCATGAAGTTGTTTTCAGTTTTCAGAGGAATGAAT    1620
GTAATAGGAAACTATGGAGTTACCAATATTGCCAACTACACTCACTCCTTAAAAAATTTATGGATATCTACAAGCTGCTTATTACCAGCA    1710
GGAGGGAAACACACTTCACACAAGAGCCTTATCAGAAACCTACCAGATGAAACTGGATATAATTTGAGACAAACAGGATGTGTTTTTTTA    1800
AACATCTGGATATCTTGTCACATTTTTGTACATTGTGACTGCTTTCAACATATACTTCATGTGTAATTATAGCTTAGACTTTAGCCTTCT    1890
TGCACTTCTGTTTTGTTTTGTTATTTGCAGTTTACAAATATAGTATTATTCTCT                                        1944
```

FIGURE 17A

```
CCCCCCCCCC CCCCCCCCCC CCNGAAGACG CCCGGAGCGG CTGCTGCAGC   50
CAGTAGCGGC CCCTTCACCG GCTGCCCCGC TCAGACCTAG TCGGGAGGGG   100
TGCGAGGCAT GCAGCTGGGG GCCCAGCTCC GGTGCCGCAC CCCGTAAAGG   150
GCTGATCTTC CACCTCGCCA CCTCAGCCAC GGGACGCCAA GACCGCATCC   200
AATTCAGACT TCTTTTGGTG CTTGTGAAAC TGAACACAAC AAAAGTATGG   250
ATATGGGAAA CCAACATCCT TCTATTAGTA GGCTTCAGGA AATCCAAAAG   300
GAAGTAAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCAGA   350
TGACAAGAAT TACAAGAAAC TGGAGAGGAT TCTAACAAAA CAGCTTTTTG   400
AAATAGACTC TGTAGATACT GAAGGAAAAG GAGATATTCA GCAAGCTAGG   450
AAGCGGGCAG CACAGGAGAC AGAACGTCTT CTCAAAGAGT TGGAGCAGAA   500
TGCAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT GAGGAAGCCC   550
AGTCCCTCGT GAGAGAGAAA ATTGTGCCAT TTTATAATGG AGGCAACTGC   600
GTAACTGATG AGTTTGAAGA AGGCATCCAA GATATCATTC TGAGGCTGAC   650
ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA   700
CTTTAACCAA AATCTGTGCG GTGCAAGAGA TAATCGAAGA CTGCATGAAA   750
AAGCAGCCTT CCCTGCCGCT TTCCGAGGAT GCACATCCTT CCGTTGCCAA   800
AATCAACTTC GTGATGTGTG AGGTGAACAA GGCCCGAGGG GTCCTGATTG   850
CACTTCTGAT GGGTGTGAAC AACAATGAGA CCTGCAGGCA CTTATCCTGT   900
GTGCTCTCGG GGCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG   950
GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT ATCAACAAAT   1000
TATTGAAATA TCTGGATTTG GAAGAGGAAG CAGACACAAC TAAAGCATTT   1050
GACCTGAGAC AGAATCATTC CATTTTAAAA ATAGAAAAGG TCCTCAAGAG   1100
AATGAGAGAA ATAAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT   1150
TGTACCTGAG CTCCAAAACA GAATTGCAGG GTTTAATTGG ACAGTTGGAT   1200
GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC   1250
AGTGATCGAG GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC   1300
```

FIGURE 17A

```
TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC   1350
GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC   1400
ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG GAAGAGCTGC   1450
TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG   1500
AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG AGGCTTGCGC AGAATATTCT   1550
CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG   1600
ATCTCACTTT TGATACTGTT TTGCACTTCA TATGTGCTTC TATGTATAGA   1650
GAGCTTTCAG TTCATTGATT TATACGTGCA TATTTCAGTC TCAGTATTTA   1700
TGATTGAAGC AAATTCTATT CAGTATCTGC TGCTTTTGAT GTTGCAAGAC   1750
AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG   1800
ATGTGGTGTG GTTTGTTTGG TTTGTCCTTT TTTTTGCGTT TTTAATCAGA   1850
AAACAAAATA GAGGCAGCTT TTGTAGATTT TAAATGGGTT GTGCAAGCAT   1900
TAAAATGCAG GTCTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA   1950
CTAGGAAAAT TATGAGAAAG GGGAAATTTT TGGTTAAATA AGAGTAAGGT   2000
TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT   2050
TTTTTTCACT TATAAGGCCT GATTGGTCCT ACCCAGCTTA ACGGGGTGGG   2100
GTTTTTTTGT TTGTTCAGAC AGTCTGTTCT TTTGTAAACA TTTTTAGTTG   2150
GAAAAACAGC ATCTGCATTT TCCCCATCCT CTACGTTTTA GAGAGGAATC   2200
TTGTTTTTGT GTGCAACATA AGAAAATTAT GAAAACTAAT AGCCAAAAAA   2250
CCTTTGAGAT TGCATTAAAG AGAAGGGATA AAGGACCAGC AATAATACCT   2300
TGTAAGTTGC TTTTGTTTGT AAAATCTGAG CTTATAGTTT TCCTTAGTGA   2350
GTAAATTCAT AAGGATGGGA ACATTTAAAT TAAGTTAATG GGCCTTTAAA   2400
AAAAAAAAAG GAAACACTCA TACCTGTAGT TGGAGGATGA ATACTGGAGA   2450
CGGGTTACCA ATGTCAGGTT ATACTAAAAC TAAATCAGAA AGTCTGAATG   2500
TAGCACATAA TGGTTCTCTT CTGTTGTCCA AGGCTGTAAA ATGGACAGCC   2550
TTGTCACACC TCCCCGGTGC TGTTTTACAA CGTGAGGGTA GACGCTGTCA   2600
```

FIGURE 17A

GTAACCCAGA GGGACCAGGC CTTCCTAGGT TTTCTAGGCA GTCAGCTGTT 2650
AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA 2700
GTGAAACCTG CTCGGAATTA AAGGCTTCCT CTGGGTGCCT GCTGAACAAC 2750
TGAGCTCATG TCATGGGCAT GTGGTGGTTT CTCTGTTGCC TGAAAGAGCC 2800
ATTAAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT 2850
CCATAAATGC TTTCTGAGGA TCCGGTACAA AATGATTTCC CAAAGTTCTG 2900
AAGTGCCTTG AGAACATGTG GGTCCGAGTG TTATAACAGA CTCCTCCCCC 2950
GGGTCACCTT TTGCCTGGTC ATCCTGTTAG AGTACATCTT TGGAAATCCA 3000
GGGTAATATT CTCTTTCAGA GATGCTCATT GTGTAACTCT GTGTAGGGAG 3050
ATAGTCACTT TAAACAGCTC AAAGTAGCTA GCTAAAGGAG TAGCCTTAAA 3100
TACCTAAAAG ATGACAGAAG CATAGCCCTT AACAAATCTT CAGCTTGTCT 3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA 3200
AATGTTCTAG AATCGCTGGA CGGTGGGGTC AGAGGGCAGT CGGTATTTAG 3250
GCCGTGAGCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCGCGGGC 3300
TCAAGGCAGG TCATTGGAAT CCACGTTTTG GCCACAGTAG TTGTAGGATT 3350
GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAAATCTT GAGGAAGAGT 3400
TTTTATTTTT TATTTATTTT TGAGATGGAG TCTCTGTTGC CCAGGCTGCA 3450
GTGCAGTGGT GCCATCTCAG CTCACTGCAA CCTCCACCTC CCAGGTTCAA 3500
GCGATTCTCC TGCCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG 3550
CACCATGCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA 3600
TGATGGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG 3650
GCCCCCCAAA GTGCTGGGAT TAACGGGTGT GAGCCACGGC GCCCAGCCCA 3700
GGAAGAGTTT TTAAATTAGA GCTCTGTTTA ATTATACCAC TGGGAAATCA 3750
TGGTTACGCT TCAGGCATAT TCTTCCCCAG AGTACTACTT ACATTTTAAA 3800
TTTCATTTTG TAAAGTTAAA TGTCAGCATT CCCTTTAAAA GTGTCCATTG 3850
TTCTTTGAAA GTAGACGTTT CAGTCATTCT TTTCAAACAA GTGTTTGTGT 3900

FIGURE 17A

```
ACCTTTTGCC AAGCTGTGGG CATCGTGTGT GAGTACAGGG TGCTCAGCTC   3950
TTCCACCGTC ATTTTGAATT GTTCACATGG GTAATTGGTC ATGGAAATGA   4000
TCAGATTGAC CTTGATTGAC TGTCAGGCAT GGCTTTGTTT CTAGTTTCAA   4050
TCTGTTCTCG TTCCTTGTAC CGGATTATTC TACTCCTGCA ATGAACCCTG   4100
TTGACACCGG ATTTAGCTCT TGTCGGCCTT CGTGGGGAGC TGTTTGTGTT   4150
AATATGAGCT ACTGCATGTA ATTCTTAAAC TGGGCTTGTC ACATTGTATT   4200
GTATTTTTGT GATCTGTAAT GAAAAGAATC TGTACTGCAA GTAAAACCTA   4250
CTCCCCAAAA ATGTGTGGCT TTGGGTCTGC ATTAAACGCT GTAGTCCATG   4300
TTCATGCC                                         4308
```

FIGURE 17B

```
MDMGNQHPSI SRLQEIQKEV KSVEQQVIGF SGLSDDKNYK KLERILTKQL   50
FEIDSVDTEG KGDIQQARKR AAQETERLLK ELEQNANHPH RIEIQNIFEE  100
AQSLVREKIV PFYNGGNCVT DEFEEGIQDI ILRLTHVKTG GKISLRKARY  150
HTLTKICAVQ EIIEDCMKKQ PSLPLSEDAH PSVAKINFVM CEVNKARGVL  200
IALLMGVNNN ETCRHLSCVL SGLIADLDAL DVCGRTEIRN YRREVVEDIN  250
KLLKYLDLEE EADTTKAFDL RQNHSILKIE KVLKRMREIK NELLQAQNPS  300
ELYLSSKTEL QGLIGQLDEV SLEKNPCIRE ARRRAVIEVQ TLITYIDLKE  350
ALEKRKLFAC EEHPSHKAVW NVLGNLSEIQ GEVLSFDGNR TDKNYIRLEE  400
LLTKQLLALD AVDPQGEEKC KAARKQAVRL AQNILSYLDL KSDEWEY     447
```

FIGURE 17C

```
CCCCCCCCCC CCCCCCCCCC CCAGAAGACG CCCGGAGCGG CTGCTGCAGC CAGTAGCGGC CCCTTCACCG GCTGCCCCGC TCAGACCTAG    90
TCGGCAGGGG TGCGAGGCAT GCAGCTGGGG GCCCAGCTCC GGTGCCGCAC CCCGTAAAGG GCTGATCTTC CACCTCGCCA CCTCAGCCAC   180
GGCACGCCAA CACCGCATCC AATTCAGACT TCTTTTGCTG CTTCTGAAAC TGAACACAAC AAAAGTATGG ATATGCCAAA CCAACATCCT   270
                                                                    M D  M C H  Q K P

TCTATTAGTA GCCTTCAGGA AATCCAAAAG CAACTAAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCACA TGACAAGAAT   360
S I S R  L Q I  I Q K  I V K S  V I Q  Q V I  G I S G  L S D  D K N

TACAAGAAAC TGGAGAGGAT TCTAACAAAA CAGCTTTTTG AAATAGACTC TGTAGATACT GAAGGAAAAG GAGATATTCA GCAAGCTAGG   450
Y K K L  I R I  L T K  Q L F I  I D S  V D T  I G K G  D I Q  Q A R

AAGCGGGCAG CACAGGAGAC AGAACGTCTT CTCAAAGAGT TGGAGCAGAA TGCAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT   540
K R A A  Q I T  I R L  L K I L  I Q N  A N K  P K R I  I I Q  N I F

GAGGAAGCCC AGTCCCTCGT GAGAGACAAA ATTGTGCCAT TTTATAATGG AGGCAACTGC GTAACTGATG AGTTTGAAGA AGGCATCCAA   630
I I A Q  S L V  R I K  I V P F  Y N G  G N C  V T D I  F I I  G I Q

GATATCATTC TGAGGCTGAC ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA CTTTAACCAA AATCTGTGCG   720
D I I L  R L T  K V K  T G G K  I S L  R K A  R Y K T  L T K  I C A

GTGCAAGAGA TAATCGAAGA CTGCATGAAA AACCAGCCTT CCCTGCCGCT TTCCGAGGAT GCACATCCTT CCGTTGCCAA AATCAACTTC   810
V Q I I  I I D  C M K  K Q P S  L P L  S I D  A K P S  V A K  I N F

GTGATGTGTG AGGTGAACAA GGCCCGAGGG GTCCTGATTG CACTTCTGAT GCCTGTGAAC AACAATGAGA CCTGCAGCCA CTTATCCTGT   900
V M C I  V N K  A R G  V L I A  L L M  G V N  N N I T  C R K  L S C

GTGCTCTCGG GCCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT   990
V L S G  L I A  D L D  A L D V  C G R  T I I  R N Y R  R I V  V I D

ATCAACAAAT TATTGAAATA TCTGGATTTG GAAGAGGAAG CAGACACAAC TAAAGCATTT GACCTGAGAC AGAATCATTC CATTTTAAAA  1080
I N K L  L K Y  L D L  I I I A  D T T  K A F  D L R Q  N N S  I L K

ATAGAAAAGG TCCTCAAGAG AATGAGAGAA ATAAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT TGTACCTGAG CTCCAAAACA  1170
I I K V  L K R  M R I  I K N I  L L Q  A Q N  P S I L  Y L S  S K T

GAATTGCAGG GTTTAATTGG ACAGTTGGAT GAGGTAAGTC TTGAAAAAAA CCCCTGCATC CGGGAAGCCA GGAGAAGAGC AGTGATCGAG  1260
I L Q G  L I G  Q L D  I V S L  I K N  P C I  R I A R  R R A  V I I

GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCCC TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAAGCC  1350
V Q T L  I T Y  I D L  K I A L  I K R  K L F  A C I I  K P S  K K A

GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTCTTTC ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG  1440
V W N V  L G N  L S I  I Q G I  V L S  F D G  N R T D  K N Y  I R L

GAAGAGCTGC TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG  1530
I I L L  T K Q  L L A  L D A V  D P Q  G I I  K C K A  A R K  Q A V

AGGCTTGCGC AGAATATTCT CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG ATCTCACTTT TGATACTGTT  1620
R L A Q  N I L  S Y L  D L K S  D I W  I Y .

TTGCACTTCA TATGTGCTTC TATGTATAGA GAGCTTTCAG TTCATTGATT TATACGTGCA TATTTCAGTC TCAGTATTTA TGATTGAAGC  1710
AAATTCTATT CAGTATCTGC TGCTTTTGAT GTTGCAAGAC AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG  1800
ATGTGCTGTG GTTTGTTTGG TTTGTCCTTT TTTTTGCGTT TTTAATCAGA AAACAAAATA GAGCCAGCTT TTGTAGATTT TAAATGCGTT  1890
GTGCAAGCAT TAAAATGCAG GTCTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA CTAGGAAAAT TATCAGAAAG GGGAAATTTT  1980
TGGTTAAATA AGAGTAAGGT TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT TTTTTTCACT TATAAGCCCT  2070
GATTGGTCCT ACCCAGCTTA ACGGGGTGGG GTTTTTTTGT TTGTTCAGAC AGTCTGTTCT TTTGTAAACA TTTTTAGTTG GAAAAACAGC  2160
ATCTGCATTT TCCCCATCCT CTACGTTTTA GACAGGAATC TTGTTTTTGT GTGCAACATA AGAAAATTAT GAAAACTAAT AGCCAAAAAA  2250
CCTTTCAGAT TGCATTAAAG AGAAGGCATA AAGGACCAGC AATAATACCT TGTAAGTTGC TTTTGTTTGT AAAATCTCAG CTTATAGTTT  2340
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CTGTTGTCCA AGGCTGTAAA ATGCACAGCC TTGTCACACC TCCCCGGTGC TGTTTTACAA CGTCAGCGTA GACGCTGTCA GTAACCCAGA  2610
GGGACCCAGGC CTTCCTAGGT TTTCTAGGCA GTCAGCTGTT AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA  2700
GTCAAACCTG CTCGGAATTA AAGCCTTCCT CTGGCTGCCT GCTCAACAAC TCAGCTCATG TCATGGGCAT GTGGTGCTTT CTCTGTTGCC  2790
TGAAAGAGCC ATTAAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT CCATAAATGC TTTCTGAGGA TCCGGTACAA  2880
AATGATTTCC CAAACTTCTG AAGTGCCTTG AGAACATGTG GGTCCGAGTG TATAAACAGA CTCCTCCCCC GGGTCACCTT TTGCCTGGTC  2970
ATCCTGTTAG AGTACATCTT TGGAAATCCA GGCTAATATT CTCTTTCAGA GATGCTCATT GTGTAACTCT GTGTAGGCAG ATAGTCACTT  3060
TAAACAGCTC AAAGTAGCTA GCTAAAGCAG TAGCCTTAAA TACCTAAAAG ATGACAGAAC CATAGCCCTT AACAAATCTT CAGCTTGTCT  3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA AATGTTCTAG AATCCCTGGA CGGTGCGGTC AGAGGGCAGT  3240
CGGTATTTAG GCCGTGACCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCCCCCGC TCAAGCCAGG TCATTGCAAT CCACGTTTTG  3330
GCCACAGTAG TTGTAGGATT GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAAATCTT GAGCAACAGT TTTTATTTTT TATTTATTTT  3420
TCAGATGGAG TCTCTGTTGC CCAGGCTGGA GTGCAGTGGT GCCATCTCAG CTCACTGCAA CCTCCACCTC CCAGGTTCAA GCCATTCTCC  3510
TGCCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG CACCATGCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA  3600
TGATGGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG GCCCCCCAAA GTGCTGGGAT TAACGGCTGT GAGCCACCGC  3690
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TCTGTTCTCG TTCCTTGTAC CGGATTATTC TACTCCTGCA ATCAACCCTG TTGACACCGG ATTTAGCTCT TGTCGGCCTT CCTGCGCACC  4140
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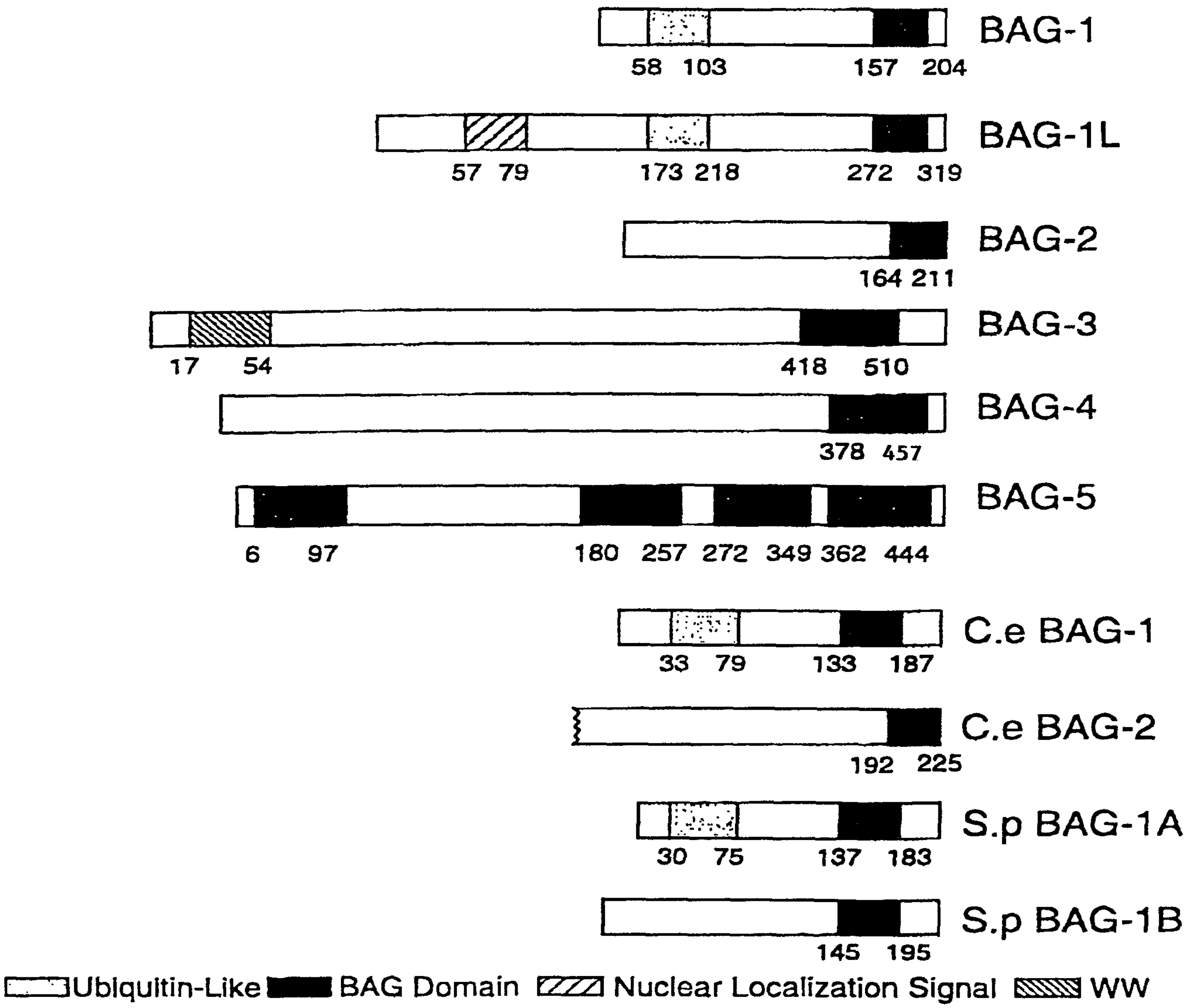
FIGURE 18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BAG-5
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C.e BAG-1
33 79 133 187
C.e BAG-2
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Ubiquitin-Like
BAG Domain
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SEQUENCE LISTING

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Takayama, Shinichi
The Burnham Institute

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Gly Gly Ala Arg Arg Pro Arg Gly Asp Arg Glu Arg Leu Gly Ser Arg
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ctg cgc gcc ctt cgg cca ggc cgg gag ccg cgc cag tcg gag ccc ccg   153
Leu Arg Ala Leu Arg Pro Gly Arg Glu Pro Arg Gln Ser Glu Pro Pro
                 25                  30                  35

gcc cag cgt ggt ccg cct ccc tct cgg cgt cca cct gcc cgg agt act   201
Ala Gln Arg Gly Pro Pro Pro Ser Arg Arg Pro Pro Ala Arg Ser Thr
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gcc agc ggg cat gac cga ccc acc agg ggc gcc gcc gcc ggc gct cgc   249
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Ala Ser Gly His Asp Arg Pro Thr Arg Gly Ala Ala Ala Gly Ala Arg
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Arg Pro Arg Met Lys Lys Lys Thr Arg Arg Arg Ser Thr Arg Ser Glu
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Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu Glu Ala Thr Trp
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agt gaa gag gcg acc cag agt gag gag gcg acc cag ggc gaa gag atg 393
Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln Gly Glu Glu Met
105 110 115

aat cgg agc cag gag gtg acc cgg gac gag gag tcg acc cgg agc gag 441
Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser Thr Arg Ser Glu
120 125 130

gag gtg acc agg gag gaa atg gcg gca gct ggg ctc acc gtg act gtc 489
Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu Thr Val Thr Val
135 140 145

acc cac agc aat gag aag cac gac ctt cat gtt acc tcc cag cag ggc 537
Thr His Ser Asn Glu Lys His Asp Leu His Val Thr Ser Gln Gln Gly
150 155 160

agc agt gaa cca gtt gtc caa gac ctg gcc cag gtt gtt gaa gag gtc 585
Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val Val Glu Glu Val
165 170 175 180

ata ggg gtt cca cag tct ttt cag aaa ctc ata ttt aag gga aaa tct 633
Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe Lys Gly Lys Ser
185 190 195

ctg aag gaa atg gaa aca ccg ttg tca gca ctt gga ata caa gat ggt 681
Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly Ile Gln Asp Gly
200 205 210

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Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro Gln Glu Glu Val
215 220 225

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Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val Glu Lys Ile Ala
230 235 240

gac cag ctg gaa gag ttg aat aaa gag ctt act gga atc cag cag ggt 825

Asp Gln Leu Glu Glu Leu Asn Lys Glu Leu Thr Gly Ile Gln Gln Gly
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ttt ctg ccc aag gat ttg caa gct gaa gct ctc tgc aaa ctt gat agg 873
Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys Lys Leu Asp Arg
265 270 275

aga gta aaa gcc aca ata gag cag ttt atg aag atc ttg gag gag att 921
Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile Leu Glu Glu Ile
280 285 290

gac aca ctg atc ctg cca gaa aat ttc aaa gac agt aga ttg aaa agg 969
Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser Arg Leu Lys Arg
295 300 305

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Lys Gly Leu Val Lys Lys Val Gln Ala Phe Leu Ala Glu Cys Asp Thr
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gtg gag cag aac atc tgc cag gag act gag cgg ctg cag tct aca aac 1065
Val Glu Gln Asn Ile Cys Gln Glu Thr Glu Arg Leu Gln Ser Thr Asn
325 330 335 340

ttt gcc ctg gcc gag tgaggtgtag cagaaaaagg ctgtgctgcc ctgaagaatg 1120
Phe Ala Leu Ala Glu
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ggcaactggc catttgccaa ttttcctact ctcacactgg ttctcaatga aaaatagtgt 1240

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35 40 45

Ala Arg Ser Thr Ala Ser Gly His Asp Arg Pro Thr Arg Gly Ala Ala
50 55 60

Ala Gly Ala Arg Arg Pro Arg Met Lys Lys Lys Thr Arg Arg Arg Ser
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Thr Arg Ser Glu Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu
85 90 95

Glu Ala Thr Trp Ser Glu Glu Ala Thr Gln Ser Glu Glu Ala Thr Gln
100 105 110

Gly Glu Glu Met Asn Arg Ser Gln Glu Val Thr Arg Asp Glu Glu Ser
115 120 125

Thr Arg Ser Glu Glu Val Thr Arg Glu Glu Met Ala Ala Ala Gly Leu
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Thr Val Thr Val Thr His Ser Asn Glu Lys His Asp Leu His Val Thr
145 150 155 160

Ser Gln Gln Gly Ser Ser Glu Pro Val Val Gln Asp Leu Ala Gln Val
165 170 175

Val Glu Glu Val Ile Gly Val Pro Gln Ser Phe Gln Lys Leu Ile Phe
180 185 190

Lys Gly Lys Ser Leu Lys Glu Met Glu Thr Pro Leu Ser Ala Leu Gly
195 200 205

Ile Gln Asp Gly Cys Arg Val Met Leu Ile Gly Lys Lys Asn Ser Pro
210 215 220

Gln Glu Glu Val Glu Leu Lys Lys Leu Lys His Leu Glu Lys Ser Val
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Glu Lys Ile Ala Asp Gln Leu Glu Glu Leu Asn Lys Glu Leu Thr Gly
245 250 255

Ile Gln Gln Gly Phe Leu Pro Lys Asp Leu Gln Ala Glu Ala Leu Cys
260 265 270

Lys Leu Asp Arg Arg Val Lys Ala Thr Ile Glu Gln Phe Met Lys Ile
275 280 285

Leu Glu Glu Ile Asp Thr Leu Ile Leu Pro Glu Asn Phe Lys Asp Ser
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Arg Leu Lys Arg Lys Gly Leu Val Lys Lys Val Gln Ala Phe Leu Ala
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ggccggtgac ctcttggcta ccccgcgtcg gaggcttag atg gct cag gcg aag 174
Met Ala Gln Ala Lys
1 5

atc aac gct aaa gcc aac gag ggg cgc ttc tgc cgc tcc tcc tcc atg 222
Ile Asn Ala Lys Ala Asn Glu Gly Arg Phe Cys Arg Ser Ser Ser Met
10 15 20

gct gac cgc tcc agc cgc ctg ctg gag agc ctg gac cag ctg gag ctc 270
Ala Asp Arg Ser Ser Arg Leu Leu Glu Ser Leu Asp Gln Leu Glu Leu
25 30 35

agg gtt gaa gct ttg aga gaa gca gca act gct gtt gag caa gag aaa 318
Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala Val Glu Gln Glu Lys
40 45 50

gaa atc ctt ctg gaa atg atc cac agt atc caa aat agc cag gac atg 366
Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln Asn Ser Gln Asp Met
55 60 65

agg cag atc agt gac gga gaa aga gaa gaa tta aat ctg act gca aac 414
Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu Asn Leu Thr Ala Asn
70 75 80 85

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Arg Leu Met Gly Arg Thr Leu Thr Val Glu Val Ser Val Glu Thr Ile
                 90                  95                 100

aga aac ccc cag cag caa gaa tcc cta aag cat gcc aca agg att att    510
Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His Ala Thr Arg Ile Ile
            105                 110                 115

gat gag gtg gtc aat aag ttt ctg gat gat ttg gga aat gcc aag agt    558
Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu Gly Asn Ala Lys Ser
        120                 125                 130

cat tta atg tcg ctc tac agt gca tgt tca tct gag gtg cca cat ggg    606
His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser Glu Val Pro His Gly
    135                 140                 145

cca gtt gat cag aag ttt caa tcc ata gta att ggc tgt gct ctt gaa    654
Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile Gly Cys Ala Leu Glu
150                 155                 160                 165

gat cag aag aaa att aag aga aga tta gag act ctg ctt aga aat att    702
Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr Leu Leu Arg Asn Ile
                170                 175                 180

gaa aac tct gac aag gcc atc aag cta tta gag cat tct aaa gga gct    750
Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu His Ser Lys Gly Ala
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ggt tcc aaa act ctg caa caa aat gct gaa agc aga ttc aat            792
Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser Arg Phe Asn
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attttaatta tctatctaga gatttttag attgaattct tgtcttgtac taggatctag 1032

catatttcac tattctgtgg atgaatacat agtttgtggg gaaaacaaac gttcagctag 1092

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Asp Gln Leu Glu Leu Arg Val Glu Ala Leu Arg Glu Ala Ala Thr Ala
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Val Glu Gln Glu Lys Glu Ile Leu Leu Glu Met Ile His Ser Ile Gln
    50                  55                  60

Asn Ser Gln Asp Met Arg Gln Ile Ser Asp Gly Glu Arg Glu Glu Leu
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Asn Leu Thr Ala Asn Arg Leu Met Gly Arg Thr Leu Thr Val Glu Val
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Ser Val Glu Thr Ile Arg Asn Pro Gln Gln Gln Glu Ser Leu Lys His
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Ala Thr Arg Ile Ile Asp Glu Val Val Asn Lys Phe Leu Asp Asp Leu
        115                 120                 125

Gly Asn Ala Lys Ser His Leu Met Ser Leu Tyr Ser Ala Cys Ser Ser
    130                 135                 140

Glu Val Pro His Gly Pro Val Asp Gln Lys Phe Gln Ser Ile Val Ile
145                 150                 155                 160

Gly Cys Ala Leu Glu Asp Gln Lys Lys Ile Lys Arg Arg Leu Glu Thr
                165                 170                 175

Leu Leu Arg Asn Ile Glu Asn Ser Asp Lys Ala Ile Lys Leu Leu Glu
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His Ser Lys Gly Ala Gly Ser Lys Thr Leu Gln Gln Asn Ala Glu Ser
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  1               5                  10                  15

gac cag aag ttt cta gcc ggc cag ttg cta cct ccc ttt atc tcc tcc      96
Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
             20                  25                  30

ttc ccc tct ggc agc gag gag gct att tcc aga cac ttc cac ccc tct     144
Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
         35                  40                  45

ctg gcc acg tca ccc ccg cct tta att cat aaa ggt gcc cgg cgc cgg     192
Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
     50                  55                  60

ctt ccc gga cac gtc ggc ggc gga gag ggg ccc acg gcg gcg gcc cgg     240
Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
 65                  70                  75                  80

cca gag act cgg cgc ccg gag cca gcg ccc cgc acc cgc gcc cca gcg     288
Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
                 85                  90                  95

ggc aga ccc caa ccc agc atg agc gcc gcc acc cac tcg ccc atg atg     336
Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
            100                 105                 110

cag gtg gcg tcc ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg     384
Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
        115                 120                 125

gag atc aag atc gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac     432
Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
    130                 135                 140

aac agc cgc acc act acg tgg aac gac ccg cgc gtg ccc tct gag ggc     480
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                165                 170                 175

agg ctg ccg cct gct agg gaa ggc cac cct gtg tac ccc cag ctc cga     576
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            180                 185                 190

cca ggc tac att ccc att cct gtg ctc cat gaa ggc gct gag aac cgg     624
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225                 230                 235                 240

cgg ggc atg cca gaa acc act cag cca gat aaa cag tgt gga cag gtg     768
Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
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gca gcg gcg gcg gca gcc cag ccc cca gcc tcc cac gga cct gag cgg     816
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    290                 295                 300

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Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305                 310                 315                 320

cca gca gcc cag ccc tcc ttc cac aaa gcc cag aag acg cac tac cca     1008
Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
                325                 330                 335

gcg cag agg ggt gag tac cag acc cac cag cct gtg tac cac aag atc     1056
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Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
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Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
        355                 360                 365

agg tca tct gtc cag ggt gca tcg agc cgg gag ggc tca cca gcc agg   1152
Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
    370                 375                 380

agc agc acg cca ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg   1200
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385                 390                 395                 400

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Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
                405                 410                 415

tcc cag cct gaa aac aaa cca gaa agt aag cca ggc cca gtt gga cca   1296
Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
            420                 425                 430

gaa ctc cct cct gga cac atc cca att caa gtg atc cgc aaa gag gtg   1344
Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val
        435                 440                 445

gat tct aaa cct gtt tcc cag aag ccc cca cct ccc tct gag aag gta   1392
Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
    450                 455                 460

gag gtg aaa gtt ccc cct gct cca gtt cct tgt cct cct ccc agc cct   1440
Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465                 470                 475                 480

ggc cct tct gct gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag   1488
Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
                485                 490                 495

agg gca gcc ccc agc act gcc cct gca gaa gct aca cct cca aaa cca   1536
Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
            500                 505                 510

gga gaa gcc gag gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa   1584
Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
        515                 520                 525

gcc atc ctg gag aag gtg cag ggg ctg gag cag gct gta gac aac ttt   1632
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Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545                 550                 555                 560

acc aaa gag ctg ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc    1728
Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
                565                 570                 575

gat gtg cgt cag gcc agg aga gac ggt gtc agg aag gtt cag acc atc    1776
Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
            580                 585                 590

ttg gaa aaa ctt gaa cag aaa gcc att gat gtc cca ggt caa gtc cag    1824
Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
        595                 600                 605

gtc tat gaa ctc cag ccc agc aac ctt gaa gca gat cag cca ctg cag    1872
Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
    610                 615                 620

gca atc atg gag atg ggt gcc gtg gca gca gac aag ggc aag aaa aat    1920
Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625                 630                 635                 640

gct gga aat gca gaa gat ccc cac aca gaa acc cag cag cca gaa gcc    1968
Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
                645                 650                 655

aca gca gca gcg act tca aac ccc agc agc atg aca gac acc cct ggt    2016
Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
            660                 665                 670

aac cca gca gca ccg tagcctctgc cctgtaaaag tcagactcgg aaccgatgtg    2071
Asn Pro Ala Ala Pro
        675

tgctttaggg attttagttg catgcatttc agagacttta ggtcagttgg ttttgattag 2131

ctgcttggta tgcagtactt gggtgaggca aacactataa agggctaaaa gggaaaatga 2191

tgcttttctt caatattctt actcttgtac aattaangaa gttgcttgtt gtttgagaag 2251

tttaaccccg ttgcttgttc tgcagccctg tcnacttggg cacccccacc acctgttagc 2311

tgtggttgtg cactgtcttt tgtagctctg gactggaggg gtagatgggg agtcaattac 2371
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ccatcacata aatatgaaac atttatcaga aatgttgcca ttttaatgag atgattttct 2431

tcatctcata attaaaatac ctgactttag agagagtaaa atgtgccagg agccatagga 2491

atatctgtat gttggatgac tttaatgcta catttth 2528

<210> 6
<211> 677
<212> PRT
<213> Homo sapiens

<400> 6
Ala Glu Leu Arg Ile Gln Pro Arg Ala Ala Ala Asn Phe Ser Gly Leu
1 5 10 15

Asp Gln Lys Phe Leu Ala Gly Gln Leu Leu Pro Pro Phe Ile Ser Ser
20 25 30

Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
35 40 45

Leu Ala Thr Ser Pro Pro Pro Leu Ile His Lys Gly Ala Arg Arg Arg
50 55 60

Leu Pro Gly His Val Gly Gly Gly Glu Gly Pro Thr Ala Ala Ala Arg
65 70 75 80

Pro Glu Thr Arg Arg Pro Glu Pro Ala Pro Arg Thr Arg Ala Pro Ala
85 90 95

Gly Arg Pro Gln Pro Ser Met Ser Ala Ala Thr His Ser Pro Met Met
100 105 110

Gln Val Ala Ser Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp
115 120 125

Glu Ile Lys Ile Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His
130 135 140

Asn Ser Arg Thr Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly
145 150 155 160

Pro Lys Glu Thr Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser
165 170 175

Arg Leu Pro Pro Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg

180 185 190

Pro Gly Tyr Ile Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg
195 200 205

Gln Val His Pro Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe
210 215 220

Arg Thr Glu Ala Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu
225 230 235 240

Arg Gly Met Pro Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val
245 250 255

Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg
260 265 270

Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala
275 280 285

Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro
290 295 300

Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg
305 310 315 320

Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro
325 330 335

Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile
340 345 350

Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe
355 360 365

Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg
370 375 380

Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val
385 390 395 400

Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val
405 410 415

Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro
420 425 430

Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val

435 440 445

Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val
450 455 460

Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro
465 470 475 480

Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu
485 490 495

Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro
500 505 510

Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu
515 520 525

Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe
530 535 540

Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu
545 550 555 560

Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala
565 570 575

Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile
580 585 590

Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln
595 600 605

Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln
610 615 620

Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn
625 630 635 640

Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala
645 650 655

Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly
660 665 670

Asn Pro Ala Ala Pro
675

<210> 7
<211> 1010
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (323)..(1009)

<400> 7
acgatatcct gtaagaccaa gaattgcaag gccagagttt gaattcttat acaaatggag 60

cgtatggtcc aacatacccc ccaggccctg gggcaaatac tgcctcatac tcaggggctt 120

attatgcacc tggttatact cagaccagtt actccacaga agttccaagt acttaccgtt 180

catctggcaa cagcccaact ccagtctctc gttggatcta tccccagcag gactgtcaag 240

actgaagcac cccctcttaa ggggcaggtt ccaggatatc cgccttcaca gaaccctgga 300

atgaccctgc cccattatcc tt atg gag atg gta atc gta gtg ttc cac aat 352
Met Glu Met Val Ile Val Val Phe His Asn
1 5 10

cac ggc cga ctg tac gac cac aag aaa gat gcg tgg gct tct cct ggt 400
His Gly Arg Leu Tyr Asp His Lys Lys Asp Ala Trp Ala Ser Pro Gly
15 20 25

gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca gcg ccc tca 448
Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser
30 35 40

gca cca ccc ggc aat ctc tac atg act gaa agt act tca cca tgg cct 496
Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro
45 50 55

agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc cag cag ccc 544
Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val Gln Gln Pro
60 65 70

aag gat tct tca tac ccc tat agc caa tca gat caa agc atg aac cgg 592
Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg
75 80 85 90

cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg ggg aca gtg 640
His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser Gly Thr Val
95 100 105

```
aac aat gat gat tca gat ctt ttg gat tcc caa gtc cag tat agt gct    688
Asn Asn Asp Asp Ser Asp Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala
            110                 115                 120

gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc aac aat caa    736
Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro Asn Asn Gln
        125                 130                 135

gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca gat gaa agt    784
Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser Asp Glu Ser
    140                 145                 150

act cct ccg agt att aaa aaa atc ata cat gtg ctg gag aag gtc cag    832
Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu Lys Val Gln
155                 160                 165                 170

tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag aca gac aaa    880
Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys Thr Asp Lys
                175                 180                 185

gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt ttg gaa ctg    928
Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu Leu Glu Leu
            190                 195                 200

gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag gcc aga aaa    976
Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln Ala Arg Lys
        205                 210                 215

gag gct gtt tgt aag att cag gcc ata ttg gaa a                      1010
Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu
    220                 225
```

<210> 8
<211> 229
<212> PRT
<213> Homo sapiens

<400> 8

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Met Glu Met Val Ile Val Val Phe His Asn His Gly Arg Leu Tyr Asp
  1               5                  10                  15

His Lys Lys Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly
             20                  25                  30

Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu
         35                  40                  45
```

Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln
50 55 60

Ser Pro Pro Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro
65 70 75 80

Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser
85 90 95

Val His Gln Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp
100 105 110

Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly
115 120 125

Asn Ala Thr Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu
130 135 140

Pro Glu Glu Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys
145 150 155 160

Lys Ile Ile His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val
165 170 175

Glu Glu Phe Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu
180 185 190

Glu Met Leu Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly
195 200 205

Gly Gln Asp Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile
210 215 220

Gln Ala Ile Leu Glu
225

<210> 9
<211> 689
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (3)..(482)

<220>
<221> unsure

<222> (105)
<223> any amino acid

<400> 9

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ga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg      47
   Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
     1               5                  10                  15

tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat     95
Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
                20                  25                  30

gag gta agt ntt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga    143
Glu Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
            35                  40                  45

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag    191
Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
        50                  55                  60

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat    239
Ala Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His
    65                  70                  75

aaa gcc gtc tgg aac gtc ctt gga aac ttg tct gag atc cag gga gaa    287
Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
 80                  85                  90                  95

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg    335
Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
                100                 105                 110

gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg    383
Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
            115                 120                 125

cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt    431
Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
        130                 135                 140

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag    479
Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
    145                 150                 155

tac tgaaatacca gagatctcac ttttgatact gttttgcact tcatatgtgc         532
Tyr
160
```

ttctatgtat agagagcttt cagttcattg atttatacgt gcatatttca gtctcagtat 592

ttatgattga agcaaattct attcagtatc tgctgctttt gatgttgcaa gacaaatatc 652

attacagcac gttaactttt ccattcggat caaaaaa 689

<210> 10
<211> 160
<212> PRT
<213> Homo sapiens

<400> 10
Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu Tyr
1 5 10 15

Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp Glu
20 25 30

Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg Ala
35 40 45

Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu Ala
50 55 60

Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His Lys
65 70 75 80

Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu Val
85 90 95

Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu Glu
100 105 110

Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro Gln
115 120 125

Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu Ala
130 135 140

Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu Tyr
145 150 155 160

<210> 11
<211> 246
<212> DNA
<213> Caenorhabditis elegans

<400> 11
atgtctttcc gcctcttcgt tgaaatattt cactttcttt tccagctttt tccccatctc 60

gacctgcttt ggtttttcga gaaaaccacg ttccaaatca gcgacatctc tcaaattgag 120

atcataggct ttttgaagat tgctcaaatt atgcttctca tattgcatga gcattttgaa 180

gcccgcgtca tcaaccaaag catttttttcc acccatcaca atgattttat cattttcttt 240

aaaatt 246

<210> 12
<211> 210
<212> PRT
<213> Caenorhabditis elegans

<400> 12
Met Lys Val Asn Val Ser Cys Ser Ser Val Gln Thr Thr Ile Asp Ile
1 5 10 15

Leu Glu Glu Asn Gln Gly Glu Asp Glu Ser Ile Leu Thr Leu Gly Gln
20 25 30

Leu Arg Asp Arg Ile Ala Thr Asp Asn Asp Val Asp Val Glu Thr Met
35 40 45

Lys Leu Leu His Arg Gly Lys Phe Leu Gln Gly Ala Asp Asp Val Ser
50 55 60

Leu Ser Thr Leu Asn Phe Lys Glu Asn Asp Lys Ile Ile Val Met Gly
65 70 75 80

Gly Lys Asn Ala Leu Val Asp Asp Ala Gly Phe Lys Met Leu Met Gln
85 90 95

Tyr Glu Lys His Asn Leu Ser Asn Leu Gln Lys Ala Tyr Asp Leu Asn
100 105 110

Leu Arg Asp Val Ala Asp Leu Glu Arg Gly Phe Leu Glu Lys Pro Lys
115 120 125

Gln Val Glu Met Gly Lys Lys Leu Glu Lys Lys Val Lys Tyr Phe Asn
130 135 140

Glu Glu Ala Glu Arg His Leu Glu Thr Leu Asp Gly Met Asn Ile Ile
145 150 155 160

```
Thr Glu Thr Thr Pro Glu Asn Gln Ala Lys Arg Asn Arg Glu Lys Arg
                165                 170                 175

Lys Thr Leu Val Asn Gly Ile Gln Thr Leu Leu Asn Gln Asn Asp Ala
            180                 185                 190

Leu Leu Arg Arg Leu Gln Glu Tyr Gln Ser Val Leu Asn Gly Asp Ile
        195                 200                 205

Pro Glu
    210


<210> 13
<211> 1377
<212> DNA
<213> Caenorhabditis elegans

<220>
<221> CDS
<222> (1)..(1377)

<400> 13
atg cca gtc gtg aac ata cca atc aaa ata ctt ggt cag aat caa tca      48
Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
  1               5                  10                  15

cat agt cga agt aac tcc tcg tct tct gtt gac aac gat cga aat caa      96
His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
             20                  25                  30

cca cca cag cag cca cct caa ccg caa cca caa cag caa tct cag caa     144
Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
         35                  40                  45

caa tac cag cag gct cca aac gtg aat acc aat atg cat cat tcc aac     192
Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
     50                  55                  60

gga ttc tca cct aac ttc cca tct cgt agt cct att ccg gac ttt ccc     240
Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
 65                  70                  75                  80

agt ttt tca tct ggg ttc cca aac gat tct gaa tgg tct tcg aat ttc     288
Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
                 85                  90                  95
```

```
ccg tcg ttt cca aat ttc cca agt gga ttc tca aat gga agt tct aat    336
Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
            100                 105                 110

ttc cct gat ttt cca aga ttc gga aga gat gga gga cta tcg cca aac    384
Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
        115                 120                 125

cca ccg atg caa gga tac agg aga agt cca aca cca aca tca act caa    432
Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
    130                 135                 140

tct cca act tct aca tta aga cgc aac tct cag cag aat caa gct cct    480
Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145                 150                 155                 160

cca caa tat tct cag caa caa cca caa caa gct caa caa cgt cag aca    528
Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
                165                 170                 175

act cct ccg tca aca aaa gct tca tct cga cca cca tct cgt act cgt    576
Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
            180                 185                 190

gaa cca aag gaa cct gag gta ccc gag aga cca gca gtt att cca ttg    624
Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
        195                 200                 205

cca tat gag aag aag gag aaa cca ctg gag aag aaa ggt agt cgt gat    672
Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
    210                 215                 220

tct gga aag ggt gat gag aac ctt gaa gag aac att gcc aag atc acg    720
Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225                 230                 235                 240

atc gga aag aat aat tgc gag tta tgt ccg gaa caa gaa acg gac ggc    768
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
                245                 250                 255

gac cca tct cca cta acc tcc cca atc acc gaa gga aag cca aag aga    816
Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
            260                 265                 270

gga aag aaa ctt caa cgt aat caa agt gtt gtt gat ttc aat gcc aag    864
Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
        275                 280                 285
```

```
aca att gtt act ttg gat aaa att gaa tta caa gtt gag cag ttg aga    912
Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
    290                 295                 300

aaa aaa gct gct gaa ctc gaa atg gaa aaa gag caa att ctt cgt tct    960
Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                 310                 315                 320

cta gga gaa atc agt gtt cat aac tgc atg ttc aaa ctg gaa gaa tgt    1008
Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                325                 330                 335

gat cgt gaa gag att gaa gca atc act gac cga ttg aca aaa aga aca    1056
Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
            340                 345                 350

aag aca gtt caa gtt gtt gtc gaa act cca cga aat gaa gaa cag aaa    1104
Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
        355                 360                 365

aaa gca ctg gaa gat gca act ttg atg atc gat gaa gtc gga gaa atg    1152
Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
    370                 375                 380

atg cat tcg aat att gaa aag gct aag ctg tgc cta caa acc tac atg    1200
Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                 390                 395                 400

aac gcc tgt tcg tac gaa gaa act gct gga gcc acc tgc caa aac ttc    1248
Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                405                 410                 415

ttg aag atc ata att cag tgc gct gct gat gat cag aaa cgc atc aag    1296
Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
            420                 425                 430

cgt cgt ctg gaa aat ctg atg tct caa att gag aat gct gag aga acg    1344
Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
        435                 440                 445

aaa gca gat ttg atg gat gat caa agc gaa tag                        1377
Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
    450                 455
```

<210> 14
<211> 458
<212> PRT

<213> Caenorhabditis elegans

<400> 14

Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
1 5 10 15

His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
20 25 30

Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
35 40 45

Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
50 55 60

Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
65 70 75 80

Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
85 90 95

Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
100 105 110

Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
115 120 125

Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
130 135 140

Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
145 150 155 160

Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
165 170 175

Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
180 185 190

Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
195 200 205

Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
210 215 220

Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
225 230 235 240

Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
245 250 255

Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
260 265 270

Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
275 280 285

Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
290 295 300

Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305 310 315 320

Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
325 330 335

Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
340 345 350

Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
355 360 365

Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
370 375 380

Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385 390 395 400

Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
405 410 415

Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
420 425 430

Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
435 440 445

Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
450 455

<210> 15
<211> 588
<212> DNA
<213> Schizosaccharomyces pombe

<220>
<221> CDS
<222> (1)..(588)

<400> 15
atg tca gaa aag act agc aca gtt aca ata cac tat gga aat cag cga 48
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
1 5 10 15

ttt ccg gta gca gtc aat cta aat gag acg tta agt gaa ctg att gat 96
Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
20 25 30

gat tta ctt gaa acg act gag att tct gag aag aaa gtc aag ctt ttt 144
Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
35 40 45

tac gct ggc aag cgt tta aaa gac aaa aaa gcc tcg tta tca aaa ttg 192
Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
50 55 60

ggt tta aaa aat cat agt aaa att cta tgt ata aga cca cat aag caa 240
Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
65 70 75 80

caa cga ggt tcc aag gaa aaa gac acg gtt gag ccc gct ccg aaa gcg 288
Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
85 90 95

gaa gcg gag aat cct gta ttt tcg cgt att tct gga gaa ata aaa gcc 336
Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
100 105 110

atc gat cag tat gtt gac aaa gaa ctt tcc ccc atg tac gac aat tac 384
Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
115 120 125

gta aat aaa ccg tcg aac gat cca aag cag aaa aac aaa cag aaa cta 432
Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
130 135 140

atg ata agt gaa cta ctt tta caa cag ctt tta aaa ttg gat gga gtt 480
Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145 150 155 160

gac gta ctg ggc agc gag aaa ttg cgt ttt gaa cgg aag caa ctt gtt 528
Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
165 170 175

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tct aag atc caa aaa atg ttg gat cac gtt gac caa aca agc caa gaa    576
Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
            180                 185                 190

gtg gcc gca tag                                                    588
Val Ala Ala
        195


<210> 16
<211> 195
<212> PRT
<213> Schizosaccharomyces pombe

<400> 16
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
  1               5                  10                  15

Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
             20                  25                  30

Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
         35                  40                  45

Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
     50                  55                  60

Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
 65                  70                  75                  80

Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
                 85                  90                  95

Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
            100                 105                 110

Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
        115                 120                 125

Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
    130                 135                 140

Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
145                 150                 155                 160

Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
                165                 170                 175
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Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
            180                 185                 190

Val Ala Ala
        195


<210> 17
<211> 621
<212> DNA
<213> Schizosaccharomyces pombe

<220>
<221> CDS
<222> (1)..(621)

<400> 17
atg tct ttt ttt acc cag ttg tgt tct atg gat aaa aaa tat tgg atc      48
Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
  1               5                  10                  15

tct cta gct gta ttg tca gtt act gtt ttg att agc gca tta ttg aaa      96
Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
             20                  25                  30

aag aga gct act gaa acc gaa gat att gtc gtt gtt cat tac gat ggc     144
Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
         35                  40                  45

gaa aag ttg aat ttt gtg ttg cga caa cca agg ctg aat atg gtt tct     192
Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
     50                  55                  60

tac act agt ttt ctt cgt cgc gtg tgc aac gca ttt tca gta atg ccc     240
Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
 65                  70                  75                  80

gac aaa gcg tct ctc aag tta aac ggg gtg acc ctc aag gat ggt tca     288
Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
                 85                  90                  95

ctt tcc gac caa aat gtg caa aat gga agt gaa tta gag ctc gaa tta     336
Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
            100                 105                 110

ccc aaa ctg agc ccg gca atg caa caa att gaa gca tat ata gat gag     384
Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
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115 120 125

ctt caa cag gat ctc gtc cct aaa att gaa gcc ttc tgc caa tcg tct 432
Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
130 135 140

ccc gct tcg gca caa gat gtt caa gat ttg cat aca cgc ctt agt gaa 480
Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145 150 155 160

aca ttg ttg gct agg atg ata aaa tta gat gct gtt aat gtt gaa gac 528
Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
165 170 175

gac cca gaa gct cgt ctt aaa aga aaa gaa gct att cgt tta tct caa 576
Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
180 185 190

caa tat ttg agt aaa cta gat tcc acc aag aat caa aac aaa tga 621
Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
195 200 205

<210> 18
<211> 206
<212> PRT
<213> Schizosaccharomyces pombe

<400> 18
Met Ser Phe Phe Thr Gln Leu Cys Ser Met Asp Lys Lys Tyr Trp Ile
1 5 10 15

Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
20 25 30

Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
35 40 45

Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
50 55 60

Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
65 70 75 80

Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
85 90 95

Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu

100 105 110

Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu
115 120 125

Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser
130 135 140

Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu
145 150 155 160

Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp
165 170 175

Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln
180 185 190

Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys
195 200 205

<210> 19
<211> 2534
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (307)..(2034)

<400> 19
gcggagctcc gcatccaacc ccgggccgcg gccaacttct ctggactgga ccagaagttt 60

ctagccggcc agttgctacc tccctttatc tcctccttcc cctctggcag cgaggaggct 120

atttccagac acttccaccc ctctctggcc acgtcacccc cgcctttaat tcataaaggt 180

gcccggcgcc ggcttcccgg acacgtcggc ggcggagagg ggcccacggc ggcggcccgg 240

ccagagactc ggcgcccgga gccagcgccc cgcacccgcg ccccagcggg cagaccccaa 300

cccagc atg agc gcc gcc acc cac tcg ccc atg atg cag gtg gcg tcc 348
Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser
1 5 10

ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg gag atc aag atc 396
Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile
15 20 25 30

gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac aac agc cgc acc 444
Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr
35 40 45

act acg tgg aac gac ccg cgc gtg ccc tct gag ggc ccc aag gag act 492
Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr
50 55 60

cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct agg ctg ccg cct 540
Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro
65 70 75

gct agg gaa ggc cac cct gtg tac ccc cag ctc cga cca ggc tac att 588
Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile
80 85 90

ccc att cct gtg ctc cat gaa ggc gct gag aac cgg cag gtg cac cct 636
Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro
95 100 105 110

ttc cat gtc tat ccc cag cct ggg atg cag cga ttc cga act gag gcg 684
Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala
115 120 125

gca gca gcg gct cct cag agg tcc cag tca cct ctg cgg ggc atg cca 732
Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro
130 135 140

gaa acc act cag cca gat aaa cag tgt gga cag gtg gca gcg gcg gcg 780
Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala
145 150 155

gca gcc cag ccc cca gcc tcc cac gga cct gag cgg tcc cag tct cca 828
Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro
160 165 170

gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc agc ctg cct tcc 876
Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser
175 180 185 190

tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg cgg ggg tac atc 924
Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile
195 200 205

tcc att ccg gtg ata cac gag cag aac gtt acc cgg cca gca gcc cag 972
Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln
210 215 220

ccc tcc ttc cac aaa gcc cag aag acg cac tac cca gcg cag agg ggt 1020
Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly
225 230 235

gag tac cag acc cac cag cct gtg tac cac aag atc cag ggg gat gac 1068
Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp
240 245 250

tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc agg tca tct gtc 1116
Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val
255 260 265 270

cag ggt gca tcg agc cgg gag ggc tca cca gcc agg agc agc acg cca 1164
Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro
275 280 285

ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg gtc gac agg cct 1212
Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro
290 295 300

cag cag ccc atg acc cat cga gaa act gca cct gtt tcc cag cct gaa 1260
Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu
305 310 315

aac aaa cca gaa agt aag cca ggc cca gtt gga cca gaa ctc cct cct 1308
Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro
320 325 330

gga cac atc cca att caa gtg atc cgc aaa gag gtg gat tct aaa cct 1356
Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro
335 340 345 350

gtt tcc cag aag ccc cca cct ccc tct gag aag gta gag gtg aaa gtt 1404
Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val
355 360 365

ccc cct gct cca gtt cct tgt cct cct ccc agc cct ggc cct tct gct 1452
Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala
370 375 380

gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag agg gca gcc ccc 1500
Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro
385 390 395

agc act gcc cct gca gaa gct aca cct cca aaa cca gga gaa gcc gag 1548
Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu
400 405 410

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gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa gcc atc ctg gag    1596
Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu
415                 420                 425                 430

aag gtg cag ggg ctg gag cag gct gta gac aac ttt gaa ggc aag aag    1644
Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys
                435                 440                 445

act gac aaa aag tac ctg atg atc gaa gag tat ttg acc aaa gag ctg    1692
Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu
            450                 455                 460

ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc gat gtg cgt cag    1740
Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln
        465                 470                 475

gcc agg aga gac ggt gtc agg aag gtt cag acc atc ttg gaa aaa ctt    1788
Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu
    480                 485                 490

gaa cag aaa gcc att gat gtc cca ggt caa gtc cag gtc tat gaa ctc    1836
Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu
495                 500                 505                 510

cag ccc agc aac ctt gaa gca gat cag cca ctg cag gca atc atg gag    1884
Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu
                515                 520                 525

atg ggt gcc gtg gca gca gac aag ggc aag aaa aat gct gga aat gca    1932
Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala
            530                 535                 540

gaa gat ccc cac aca gaa acc cag cag cca gaa gcc aca gca gca gcg    1980
Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala
        545                 550                 555

act tca aac ccc agc agc atg aca gac acc cct ggt aac cca gca gca    2028
Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala
    560                 565                 570

ccg tag cctctgccct gtaaaaatca gactcggaac cgatgtgtgc tttagggaat     2084
Pro
575

tttaagttgc atgcatttca gagactttaa gtcagttggt ttttattagc tgcttggtat 2144

gcagtaactt gggtggaggc aaaacactaa taaaagggct aaaaaggaaa atgatgcttt 2204
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tcttctatat tcttactctg tacaaataaa gaagttgctt gttgtttgag aagtttaacc 2264

ccgttgcttg ttctgcagcc ctgtctactt gggcaccccc accacctgtt agctgtggtt 2324

gtgcactgtc ttttgtagct ctggactgga ggggtagatg gggagtcaat tacccatcac 2384

ataaatatga aacatttatc agaaatgttg ccattttaat gagatgattt tcttcatctc 2444

ataattaaaa tacctgactt tagagagagt aaaatgtgcc aggagccata ggaatatctg 2504

tatgttggat gactttaatg ctacattttc 2534

<210> 20
<211> 575
<212> PRT
<213> Homo sapiens

<400> 20
Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser Gly Asn
1 5 10 15

Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile Asp Pro
20 25 30

Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr Thr Thr
35 40 45

Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr Pro Ser
50 55 60

Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro Ala Arg
65 70 75 80

Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile Pro Ile
85 90 95

Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro Phe His
100 105 110

Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala Ala Ala
115 120 125

Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro Glu Thr
130 135 140

Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala Ala Ala

145 150 155 160

Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro Ala Ala
165 170 175

Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser Ser Gly
180 185 190

Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile Ser Ile
195 200 205

Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln Pro Ser
210 215 220

Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly Glu Tyr
225 230 235 240

Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp Trp Glu
245 250 255

Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val Gln Gly
260 265 270

Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro Leu His
275 280 285

Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro Gln Gln
290 295 300

Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu Asn Lys
305 310 315 320

Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro Gly His
325 330 335

Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro Val Ser
340 345 350

Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val Pro Pro
355 360 365

Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala Val Pro
370 375 380

Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro Ser Thr
385 390 395 400

Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu Ala Pro

405 410 415

Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu Lys Val
420 425 430

Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys Thr Asp
435 440 445

Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu Leu Ala
450 455 460

Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln Ala Arg
465 470 475 480

Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu Glu Gln
485 490 495

Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu Gln Pro
500 505 510

Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu Met Gly
515 520 525

Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala Glu Asp
530 535 540

Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala Thr Ser
545 550 555 560

Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala Pro
565 570 575

<210> 21
<211> 1966
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (43)..(1416)

<400> 21
cggtgggagc ggggcgggaa gcgcttcagg gcagcggatc cc atg tcg gcc ctg 54
Met Ser Ala Leu
1

agg cgc tcg ggc tac ggc ccc agt gac ggt ccg tcc tac ggc cgc tac 102

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Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser Tyr Gly Arg Tyr
  5                  10                  15                  20

tac ggg cct ggg ggt gga gat gtg ccg gta cac cca cct cca ccc tta      150
Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro Pro Pro Pro Leu
                25                  30                  35

tat cct ctt cgc cct gaa cct ccc cag cct ccc att tcc tgg cgg gtg      198
Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile Ser Trp Arg Val
            40                  45                  50

cgc ggg ggc ggc ccg gcg gag acc acc tgg ctg gga gaa ggc gga gga      246
Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly Glu Gly Gly Gly
        55                  60                  65

ggc gat ggc tac tat ccc tcg gga ggc gcc tgg cca gag cct ggt cga      294
Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro Glu Pro Gly Arg
    70                  75                  80

gcc gga gga agc cac cag gag cag cca cca tat cct agc tac aat tct      342
Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro Ser Tyr Asn Ser
 85                  90                  95                 100

aac tat tgg aat tct act gcg aga tct agg gct cct tac cca agt aca      390
Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro Tyr Pro Ser Thr
                105                 110                 115

tat cct gta aga cca gaa ttg caa ggc cag agt ttg aat tct tat aca      438
Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu Asn Ser Tyr Thr
            120                 125                 130

aat gga gcg tat ggt cca aca tac ccc cca ggc cct ggg gca aat act      486
Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro Gly Ala Asn Thr
        135                 140                 145

gcc tca tac tca ggg gct tat tat gca cct ggt tat act cag acc agt      534
Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr Thr Gln Thr Ser
    150                 155                 160

tac tcc aca gaa gtt cca agt act tac cgt tca tct ggc aac agc cca      582
Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser Gly Asn Ser Pro
165                 170                 175                 180

act cca gtc tct cgt tgg atc tat ccc cag cag gac tgt cag act gaa      630
Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp Cys Gln Thr Glu
                185                 190                 195

gca ccc cct ctt agg ggg cag gtt cca gga tat ccg cct tca cag aac      678
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Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro Pro Ser Gln Asn
            200                 205                 210

cct gga atg acc ctg ccc cat tat cct tat gga gat ggt aat cgt agt    726
Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp Gly Asn Arg Ser
        215                 220                 225

gtt cca caa tca gga ccg act gta cga cca caa gaa gat gcg tgg gct    774
Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu Asp Ala Trp Ala
    230                 235                 240

tct cct ggt gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca    822
Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser
245                 250                 255                 260

gcg ccc tca gca cca ccc ggc aat ctc tac atg act gaa agt act tca    870
Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser
                265                 270                 275

cca tgg cct agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc    918
Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val
            280                 285                 290

cag cag ccc aag gat tct tca tac ccc tat agc caa tca gat caa agc    966
Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser
        295                 300                 305

atg aac cgg cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg    1014
Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser
    310                 315                 320

ggg aca gtg atc aat gaa gat tca gat ctt ttg gat tcc caa gtc cag    1062
Gly Thr Val Ile Asn Glu Asp Ser Asp Leu Leu Asp Ser Gln Val Gln
325                 330                 335                 340

tat agt gct gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc    1110
Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro
                345                 350                 355

aac aat caa gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca    1158
Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser
            360                 365                 370

gat gaa agt act cct ccg agt att aaa aaa atc ata cat gtg ctg gag    1206
Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu
        375                 380                 385

aag gtc cag tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag    1254
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Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys
390 395 400

aca gac aaa gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt 1302
Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu
405 410 415 420

ttg gaa ctg gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag 1350
Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln
425 430 435

gcc aga aaa gag gct gtt tgt aag att cag gcc ata ctg gaa aaa tta 1398
Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu Lys Leu
440 445 450

gaa aaa aaa gga tta tga aaggatttag aacaaagtgg aagcctgtta 1446
Glu Lys Lys Gly Leu
455

ctaacttgac caaagaacac ttgattaggt taattaccct ctttttgaaa tgcctgttga 1506

tgacaagaag caatacattc cagcttttcc tttgatttta tacttgaaaa actggcaaag 1566

gaatggaaga atattttagt catgaagttg ttttcagttt tcagacgaat gaatgtaata 1626

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tctacaagct gcttattacc agcaggaggg aaacacactt cacacaacag gcttatcaga 1746

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Glu Pro Gly Arg Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :07N 21/02; C07K 1/00
US CL :530/387.1, 350; 435/6, 7/1; 536/23.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 350; 435/6, 7/1; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,652,223 A (KOHN ET AL) 29 July 1997(29/7/97) see entire document.	2-5, 14, 32-34
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA693697, HILLIER, L. ET AL. 'WashU-NCI human EST Project,' 16 December 1997, see entire reference.	2
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA456862, NCI_CGAP, 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index,' 15 August 1997, see entire reference.	2,4

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 NOVEMBER 1999	19 JAN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
SHEILA J. HUFF
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/21053

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1, 13, 24, 25
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No meaningful search could be carried out because no limitations could be placed on the sequence

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest

☐ No protest accompanied the payment of additional search fees

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Genbank, National Center for Biotech. Info., Accession No. G29287, MYERS, R.M., 04 October 1996, see entire reference.	2,4
X	Database Genbank, National Center for Biotech. Info., Accession No. G06974, HUDSON, T., "Whitehead Institute.MIT Center for Genome Research,'19 October 1995, see entire reference.	2,4
X	Database Genseq, Derwent, Alexandria, Virginia, Accession No. V81267, OTSUKA PHARM CO LTD, 'New Bcl-2 interaction prrtein gene (Bis)- useful for elucidation of the molecular mechanism of apoptosis, and in diagnosis, prevention and treatment of diseases,' 15 December 1998 see enire reference.	2-5
X	Database, Geneseq, Derwent, Alexandria, Virginia, Accession No. T19051, MATSUBARA ET AL., "Identifying gene signatures in 3'-directed human cDNA library,' 01 June 1995, see entire reference.	2,4
X	Database Geneseq, Derwent, Alexandria, Virginia, Accession No. Q90296, LA JOLLA CANCER RES FOUN. 'Human Bcl-2-associated protein BAG-1 cDNA,'18 May 1995 see entire reference.	2-5,14